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(54) Title: CARVEDILOL HYDOBROMIDE

(57) Abstract: The present invention relates to a salt of carvedilol, corresponding compositions containing such a carvedilol salt or corresponding solvates thereof, and/or methods of using the aforementioned compound(s) in the treatment of certain disease states in mammals, in particular man. The present invention further relates to a novel crystalline form of carvedilol hydrobromide, which is the hydrobromide salt of 1-(carbazol-4-yloxy-3-[[2-(omethoxyphenoxy)ethyl]amino]-2-propanol, and/or other carvedilol solvates thereof, compositions containing salts or solvates of carvedilol hydrobromide, and methods of using the aforementioned compound(s) to treat hypertension, congestive heart failure, and angina, etc.

Carvedilol Hydrobromide

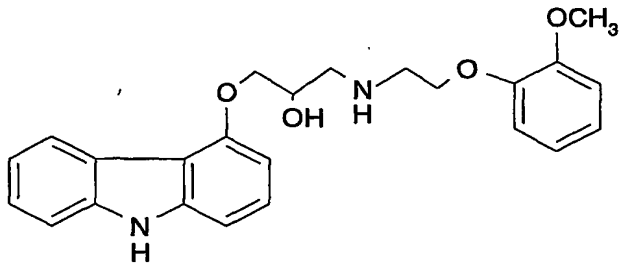
Field of the Invention

The present invention relates to a salt of carvedilol, corresponding compositions containing such a carvedilol salt or corresponding solvates thereof, and/or methods of using the aforementioned compound(s) in the treatment of certain disease states in mammals, in particular man.

The present invention further relates to a novel crystalline form of carvedilol hydrobromide, which is the hydrobromide salt of 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, and/or other carvedilol hydrobromide solvates thereof, compositions containing such salts and/or solvates of carvedilol hydrobromide, and methods of using the aforementioned salt(s) and/or solvate(s) to treat hypertension, congestive heart failure, and angina, etc.

Background of the Invention

The compound, 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy) ethyl]-amino]-2-propanol is known as Carvedilol. Carvedilol is depicted by the following chemical structure:



Carvedilol is disclosed in U.S. Patent No. 4,503,067 to Wiedemann et al. (i.e., assigned to Boehringer Mannheim, GmbH, Mannheim-Waldhof, Fed. Rep. of Germany), which was issued on March 5, 1985.

Currently, Carvedilol is synthesized as free base for incorporation in medication that is available commercially. The aforementioned free base form of Carvedilol is a racemic mixture of R(+) and S(-) enantiomers, where

nonselective β-adrenoreceptor blocking activity is exhibited by the S(-) enantiomer and α-adrenergic blocking activity is exhibited by both R(+) and S(-) enantiomers. Those unique features or characteristics associated with such a racemic Carvedilol mixture contributes to two complementary pharmacologic actions: i.e., mixed venous and arterial vasodilation and non-cardioselective, beta-adrenergic blockade.

Carvedilol is used for treatment of hypertension, congestive heart failure and angina. The currently commercially available carvedilol product is a conventional, tablet prescribed as a twice-a-day medication in the United States.

Carvedilol contains an α-hydroxyl secondary amine functional group, which has a pKa of 7.8. Carvedilol exhibits predictable solubility behaviour in neutral or alkaline media, i.e. above a pH of 9.0, the solubility of carvedilol is relatively low (< 1 µg/mL). The solubility of carvedilol increases with decreasing pH and reaches a plateau near pH = 5, i.e. where saturation solubility is about 23 µg/mL at pH 7 and about 100 µg/mL at pH = 5 at room temperature. At lower pH values (i.e., at a pH of 1 to 4 in various buffer systems), solubility of carvedilol is limited by the solubility of its protonated form or its corresponding salt formed *in-situ*. The hydrochloride salt of carvedilol generated *in-situ* in an acidic medium, such as in a simulated gastric fluid, is less soluble in such medium than the protonated form of carvedilol.

In light of the foregoing, a salt, and/or novel crystalline form of carvedilol (i.e., such as carvedilol hydrobromide monohydrate, carvedilol hydrobromide anhydrate, and/or other solvates thereof) with greater aqueous solubility, chemical stability, etc. would offer many potential benefits for provision of medicinal products containing the drug carvedilol. Such benefits would include products with the ability to achieve desired or prolonged drug levels in a systemic system by sustaining absorption along the gastro-intestinal tract of mammals (i.e., such as humans), particularly in regions of neutral pH, where a drug, such as carvedilol, has minimal solubility.

Surprisingly, it has now been shown that a novel crystalline form of

carvedilol hydrobromide salt, can be isolated as a pure, crystalline solid, which exhibits much higher aqueous solubility than the corresponding free base or other prepared crystalline salts of carvedilol, such as the hydrochloride salt. This novel crystalline form also has potential to improve the stability of carvedilol in formulations due to the fact that the secondary amine functional group attached to the carvedilol core structure, a moiety pivotal to degradation processes, is protonated as a salt.

In light of the above, a need exists to develop different carvedilol forms and/or different compositions respectively, which have greater aqueous solubility, chemical stability, sustained or prolonged drug or absorption levels (i.e., such as in neutral gastrointestinal tract pH regions, etc.).

There also exists a need to develop methods of treatment for hypertension, congestive heart failure or angina, etc. which comprises administration of the aforementioned compounds and/or compositions.

The present invention is directed to overcoming these and other problems encountered in the art.

Summary of the Invention

In general, the present invention relates to a salt of carvedilol, corresponding compositions containing such a carvedilol salt or corresponding solvates thereof, and/or methods of using the aforementioned compound(s) in the treatment of certain disease states in mammals, in particular man.

More specifically, the present invention provides a salt, and/or novel crystalline form of carvedilol hydrobromide (i.e., such as carvedilol hydrobromide monohydrate, carvedilol hydrobromide anhydrate), and/or other solvates thereof.

The present invention further relates to pharmaceutical compositions, which contain the aforementioned salt and/or novel crystalline forms and/or solvates of carvedilol hydrobromide.

The present invention relates to a method of treating hypertension, congestive heart failure or angina, which comprises administering to a subject in need thereof an effective amount of a salt and/or novel crystalline form of carvedilol (i.e., as defined by the aforementioned salts and/or solvates) or a corresponding pharmaceutical composition, which contains such aforementioned salt, and/or novel crystalline forms of carvedilol., etc.

Brief Description of the Figures

Figure 1 is an x-ray powder diffractogram for carvedilol hydrobromide monohydrate.

Figure 2 is a differential scanning calorimetry thermogram for carvedilol hydrobromide monohydrate.

Figure 3 is an FT-Raman spectrum for carvedilol hydrobromide monohydrate.

Figure 4 is an FT-Raman spectrum for carvedilol hydrobromide monohydrate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 5 is an FT-Raman spectrum for carvedilol hydrobromide monohydrate in the 2000-400 cm^{-1} region of the spectrum.

Figure 6 is an FT-IR spectrum for carvedilol hydrobromide monohydrate.

Figure 7 is an FT-IR spectrum for carvedilol hydrobromide monohydrate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 8 is an FT-IR spectrum for carvedilol hydrobromide monohydrate in the 2000-500 cm^{-1} region of the spectrum.

Figure 9 is a view of a single molecule of carvedilol hydrobromide monohydrate. The hydroxyl group and the water molecule are disordered.

Figure 10 are views of molecules of carvedilol hydrobromide monohydrate showing the N-H···Br···H-N interactions. The top view focuses on Br1 and the bottom view focuses on Br2. The interaction between the carvedilol cation and the bromine anion is unusual. Each carvedilol molecule makes two chemically different contacts to the bromine anions. Each bromine anion sits on a crystallographic special position (that is, on a crystallographic two-fold axis) which means that there are two half bromine anions interacting

with each carvedilol cation.

Figure 11 is a differential scanning calorimetry thermogram for carvedilol hydrobromide dioxane solvate.

Figure 12 is an FT-Raman spectrum for carvedilol hydrobromide dioxane solvate.

Figure 13 is an FT-Raman spectrum for carvedilol hydrobromide dioxane solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 14 is an FT-Raman spectrum for carvedilol hydrobromide dioxane solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 15 is an FT-IR spectrum for carvedilol hydrobromide dioxane solvate.

Figure 16 is an FT-IR spectrum for carvedilol hydrobromide dioxane solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 17 is an FT-IR spectrum for carvedilol hydrobromide dioxane solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 18 is a differential scanning calorimetry thermogram for carvedilol hydrobromide 1-pentanol solvate.

Figure 19 is an FT-Raman spectrum for carvedilol hydrobromide 1-pentanol solvate.

Figure 20 is an FT-Raman spectrum for carvedilol hydrobromide 1-pentanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 21 is an FT-Raman spectrum for carvedilol hydrobromide 1-pentanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 22 is an FT-IR spectrum for carvedilol hydrobromide 1-pentanol solvate.

Figure 23 is an FT-IR spectrum for carvedilol hydrobromide 1-pentanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 24 is an FT-IR spectrum for carvedilol hydrobromide 1-pentanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 25 is a differential scanning calorimetry thermogram for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 26 is an FT-Raman spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 27 is an FT-Raman spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 28 is an FT-Raman spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 29 is an FT-IR spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 30 is an FT-IR spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 31 is an FT-IR spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 32 is a differential scanning calorimetry thermogram for carvedilol hydrobromide trifluoroethanol solvate.

Figure 33 is an FT-Raman spectrum for carvedilol hydrobromide trifluoroethanol solvate.

Figure 34 is an FT-Raman spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 35 is an FT-Raman spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 36 is an FT-IR spectrum for carvedilol hydrobromide trifluoroethanol solvate.

Figure 37 is an FT-IR spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 38 is an FT-IR spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 39 is a differential scanning calorimetry thermogram for carvedilol hydrobromide 2-propanol solvate.

Figure 40 is an FT-Raman spectrum for carvedilol hydrobromide 2-propanol solvate.

Figure 41 is an FT-Raman spectrum for carvedilol hydrobromide 2-

propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 42 is an FT-Raman spectrum for carvedilol hydrobromide 2-propanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 43 is an FT-IR spectrum for carvedilol hydrobromide 2-propanol solvate.

Figure 44 is an FT-IR spectrum for carvedilol hydrobromide 2-propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 45 is an FT-IR spectrum for carvedilol hydrobromide 2-propanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 46 is an x-ray powder diffractogram for carvedilol hydrobromide n-propanol solvate #1.

Figure 47 shows the thermal analysis results for carvedilol hydrobromide n-propanol solvate #1.

Figure 48 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #1.

Figure 49 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 50 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 2000-400 cm^{-1} region of the spectrum.

Figure 51 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #1.

Figure 52 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 53 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 2000-500 cm^{-1} region of the spectrum.

Figure 54 is an x-ray powder diffractogram for carvedilol hydrobromide n-propanol solvate #2.

Figure 55 shows the thermal analysis results for carvedilol hydrobromide n-propanol solvate #2.

Figure 56 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #2.

Figure 57 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 58 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 2000-400 cm^{-1} region of the spectrum.

Figure 59 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #2.

Figure 60 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 61 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 2000-500 cm^{-1} region of the spectrum.

Figure 62 is an x-ray powder diffractogram for carvedilol hydrobromide anhydrous.

Figure 63 shows the thermal analysis results for carvedilol hydrobromide anhydrous.

Figure 64 is an FT-Raman spectrum for carvedilol hydrobromide anhydrous.

Figure 65 is an FT-Raman spectrum for carvedilol hydrobromide anhydrous in the 4000-2000 cm^{-1} region of the spectrum.

Figure 66 is an FT-Raman spectrum for carvedilol hydrobromide anhydrous in the 2000-400 cm^{-1} region of the spectrum.

Figure 67 is an FT-IR spectrum for carvedilol hydrobromide anhydrous.

Figure 68 is an FT-IR spectrum for carvedilol hydrobromide anhydrous in the 4000-2000 cm^{-1} region of the spectrum.

Figure 69 is an FT-IR spectrum for carvedilol hydrobromide anhydrous in the 2000-500 cm^{-1} region of the spectrum.

Figure 70 is an x-ray powder diffractogram for carvedilol hydrobromide ethanol solvate.

Figure 71 shows the thermal analysis results for carvedilol hydrobromide ethanol solvate.

Figure 72 is an FT-Raman spectrum for carvedilol hydrobromide ethanol solvate.

Figure 73 is an FT-Raman spectrum for carvedilol hydrobromide ethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 74 is an FT-Raman spectrum for carvedilol hydrobromide ethanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 75 is an FT-IR spectrum for carvedilol hydrobromide ethanol solvate.

Figure 76 is an FT-IR spectrum for carvedilol hydrobromide ethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 77 is an FT-IR spectrum for carvedilol hydrobromide ethanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 78 is an x-ray powder diffractogram for carvedilol hydrobromide dioxane solvate.

Figure 79 is an x-ray powder diffractogram for carvedilol hydrobromide 1-pentanol solvate.

Figure 80 is an x-ray powder diffractogram for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 81 is an x-ray powder diffractogram for carvedilol hydrobromide trifluoroethanol solvate.

Figure 82 is an x-ray powder diffractogram for carvedilol hydrobromide 2-propanol solvate.

Detailed Description of the Invention

The present invention provides a salt and/or novel crystalline form of carvedilol, i.e., such as carvedilol hydrobromide monohydrate, carvedilol hydrobromide anhydrate, and/or other solvates thereof.

The present invention relates to a pharmaceutical composition, which comprises the aforementioned salts and/or solvates of carvedilol and a pharmaceutically acceptable carrier.

The present invention relates to a method of treating hypertension, congestive heart failure or angina, which comprises administering to a subject in need thereof an effective amount of a salt and/or novel crystalline form of carvedilol (i.e., as defined by the aforementioned salts and/or solvates) or a

corresponding pharmaceutical composition, which contains such aforementioned salt, and/or novel crystalline forms of carvedilol.

Carvedilol is disclosed and claimed in U.S. Patent No. 4,503,067 to Wiedemann et al. ("U.S. '067 Patent"). Reference should be made to U.S. '067 Patent for its full disclosure, which include methods of preparing and/or using the carvedilol compound, etc. The entire disclosure of the U.S. '067 Patent is incorporated hereby by reference in its entirety.

The present invention relates to a compound, which is a salt of carvedilol hydrobromide (such as crystalline carvedilol hydrobromide monohydrate), and/or a carvedilol solvate thereof.

In accordance with the present invention, it has been found unexpectedly that carvedilol hydrobromide can be isolated readily as a novel crystalline form, which displays much higher solubility when compared to the free base of carvedilol.

In particular, crystalline carvedilol hydrobromide monohydrate of the present invention can be prepared by crystallization from an acetone-water solvent system containing carvedilol and hydrobromic acid.

In accordance with the present invention suitable solvates of the instant invention may be prepared by preparing a slurry of the carvedilol hydrobromide salt in a solvent, such as dioxane, 1-pentanol, 2-methyl-1-propanol, trifluoroethanol, 2-propanol and n-propanol.

Suitable solvates of carvedilol as defined in the present invention, include, but are not limited to carvedilol hydrobromide 1-pentanol solvate, carvedilol hydrobromide 2-methyl-1-pentanol solvate, carvedilol hydrobromide trifluoroethanol solvate, carvedilol hydrobromide 2-propanol solvate, carvedilol hydrobromide n-propanol solvate #1, carvedilol hydrobromide n-propanol solvate #2, carvedilol hydrobromide ethanol solvate, carvedilol hydrobromide anhydrate, etc.

In the present invention, carvedilol hydrobromide anhydrate can be prepared by dissolving carvedilol in a solvent, such as dichloromethane, acetonitrile or isopropyl acetate, followed by the addition of anhydrous HBr

(HBr in acetic acid or gaseous HBr).

It is recognized that the compounds of the present invention may exist in forms as stereoisomers, regioisomers, or diastereiomers, etc. These compounds may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. For example, carvedilol may exist as as racemic mixture of R(+) and S(-) enantiomers, or in separate respectively optically forms, i.e., existing separately as either the R(+) enantiomer form or in the S(+) enantiomer form. All of these individual compounds, isomers, and mixtures thereof are included within the scope of the present invention.

According to the instant invention, the various forms of carvedilol hydrobromide and/or corresponding solvates are distinguished from each other using different spectroscopic identification techniques, such as Infrared (IR), Raman, Differential Scanning Calorimetry (DSC) and X-ray powder diffraction, etc.

Specifically, a salt or novel crystalline form of carvedilol, which includes carvedilol hydrobromide monohydrate, anhydrate, and/or other solvates thereof, are characterized by spectroscopic data as described below and depicted in Figures 1-82.

For example, crystalline carvedilol hydrobromide monohydrate (see, Example 1: Form 1) is identified by an x-ray diffraction pattern as shown substantially in Figure 1, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 6.5 ± 0.2 (2θ), 10.3 ± 0.2 (2θ), 15.7 ± 0.2 (2θ), 16.3 ± 0.2 (2θ), 19.8 ± 0.2 (2θ), 20.1 ± 0.2 (2θ), 21.9 ± 0.2 (2θ), 25.2 ± 0.2 (2θ), and 30.6± 0.2 (2θ).

Crystalline carvedilol hydrobromide dioxane solvate (see, Example 2: Form 2) also is identified by an x-ray diffraction pattern as shown substantially in Figure 78, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 7.7 ± 0.2 (2θ), 8.4 ± 0.2 (2θ), 15.6 ± 0.2 (2θ), 17.0 ± 0.2 (2θ), 18.7 ± 0.2 (2θ), 19.5 ± 0.2 (2θ), 21.4 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 27.9 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide 1-pentanol solvate (see, Example 3: Form 3) also is identified by an x-ray diffraction pattern as shown substantially

in Figure 79, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 77.5 ± 0.2 (2θ), 7.8 ± 0.2 (2θ), 15.2 ± 0.2 (2θ), 18.9 ± 0.2 (2θ), 22.1 ± 0.2 (2θ), and 31.4 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide 2-methyl-1-propanol solvate (see, Example 4: Form 4) also is identified by an x-ray diffraction pattern as shown substantially in Figure 80, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 7.8 ± 0.2 (2θ), 8.1 ± 0.2 (2θ), 16.3 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), and 28.5 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide trifluoroethanol solvate (see, Example 5: Form 5) also is identified by an x-ray diffraction pattern as shown substantially in Figure 81, which depicts characteristic peaks in degrees two-theta (2θ): i.e.,. 7.7 ± 0.2 (2θ), 8.4 ± 0.2 (2θ), 15.6 ± 0.2 (2θ), 16.9 ± 0.2 (2θ), 18.9 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), 23.8 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 32.7 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide 2-propanol solvate (see, Example 6: Form 6) also is identified by an x-ray diffraction pattern as shown substantially in Figure 82, which depicts characteristic peaks in degrees two-theta (2θ): i.e.,. 7.9 ± 0.2 (2θ), 8.3 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.7 ± 0.2 (2θ), 23.2 ± 0.2 (2θ), 23.6 ± 0.2 (2θ), and 32.1 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide n-propanol solvate #1 (see, Example 7: Form 7) also is identified by an x-ray diffraction pattern as shown substantially in Figure 46, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 7.9 ± 0.2 (2θ), 8.5 ± 0.2 (2θ), 17.0 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.6 ± 0.2 (2θ), 23.1 ± 0.2 (2θ), 23.6 ± 0.2 (2θ), and 21.2 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide n-propanol solvate #2 (see, Example 8: Form 8) also is identified by an x-ray diffraction pattern as shown substantially in Figure 54, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 8.0 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.6 ± 0.2 (2θ), 23.1 ± 0.2 (2θ), 25.9 ± 0.2 (2θ), 27.2 ± 0.2 (2θ), 30.6 ± 0.2 (2θ), and 32.2 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide anhydrous (see, Example 9: Form 9) also is identified by an x-ray diffraction pattern as shown substantially in Figure

62, which depicts characteristic peaks in degrees two-theta (2θ): i.e.,. 6.6 ± 0.2 (2θ), 16.1 ± 0.2 (2θ), 17.3 ± 0.2 (2θ), 21.2 ± 0.2 (2θ), 22.1 ± 0.2 (2θ), 24.1 ± 0.2 (2θ), and 27.9 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide ethanol solvate (see, Example 10: Form 10) also is identified by an x-ray diffraction pattern as shown substantially in Figure 70, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 8.1 ± 0.2 (2θ), 8.6 ± 0.2 (2θ), 13.2 ± 0.2 (2θ), 17.4 ± 0.2 (2θ), 18.6 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), 23.2 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 27.4 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide monohydrate further is identified by an infrared spectrum as shown substantially in Figure 6.

Carvedilol hydrobromide anhydrate also an infrared spectrum which comprises characteristic absorption bands expressed in wave numbers as shown substantially in Figure 67.

Crystalline carvedilol hydrobromide monohydrate is identified also by a Raman spectrum as shown substantially in Figure 3.

Carvedilol hydrobromide anhydrate also a Raman spectrum which comprises characteristic peaks as shown substantially in Figure 64.

Further, the present invention relates to pharmaceutical compositions, which contain the aforementioned salt and/or novel crystalline forms and/or solvates of carvedilol hydrobromide.

Importantly, the chemical and/or physical properties of carvedilol forms described herein, which include salt and/or novel crystalline forms of carvedilol, indicate that those forms may be particularly suitable for inclusion in medicinal agents, pharmaceutical compositions, etc.

For example, solubility of various carvedilol salts, anhydrates, and/or solvates as those described herein may facilitate provision or development of a dosage form from which the drug substance becomes available for bioabsorption throughout the gastrointestinal tract (i.e., in particular the lower small intestine and colon). In light of the foregoing, it may be possible to develop stable controlled release dosage forms containing such carvedilol hydrobromide monohydrate, anhydrates and/or solvates, etc., for once-per-day

dosage, delayed release or pulsatile release to optimize therapy by matching pharmacokinetic performance with pharmacodynamic requirements.

Compounds or compositions within the scope of this invention include all compounds or compositions, wherein the compound of the present invention is contained in an amount effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art.

Moreover, the quantity of the compound or composition of the present invention administered will vary depending on the patient and the mode of administration and can be any effective amount.

Treatment regimen for the administration of the compounds and/or compositions of the present invention can also be determined readily by those with ordinary skill in art. The quantity of the compound and/or composition of the present invention administered may vary over a wide range to provide in a unit dosage an effective amount based upon the body weight of the patient per day to achieve the desired effect.

In particular, a composition of the present invention is presented as a unit dose and taken preferably from 1 to 2 times daily, most preferably once daily to achieve the desired effect.

Depending upon the treatment being effected, the compounds, and/or or compositions of the present invention can be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Preferably, the composition is adapted for oral administration.

In general, pharmaceutical compositions of the present invention are prepared using conventional materials and techniques, such as mixing, blending and the like.

In accordance with the present invention, compounds and/or pharmaceutical composition can also include, but are not limited to, suitable adjuvants, carriers, excipients, or stabilizers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions, or emulsions.

Typically, the composition will contain a compound of the present

invention, such as a salt of carvedilol or active compound(s), together with the adjuvants, carriers and/or excipients. In particular, a pharmaceutical composition of the present invention comprises an effective amount of a salt of carvedilol (i.e., such as carvedilol hydrobromide monohydrate), corresponding solvates (i.e., as identified herein) and/or anhydrates (i.e., carvedilol anhydrate) thereof, with any of the characteristics noted herein, in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents thereof, and if desired, other active ingredients.

In accordance with the present invention, solid unit dosage forms can be conventional types known in the art. The solid form can be a capsule and the like, such as an ordinary gelatin type containing the compounds of the present invention and a carrier, for example, lubricants and inert fillers such as, lactose, sucrose, or cornstarch. In another embodiment, these compounds are tableted with conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders like acacia, cornstarch, or gelatin, disintegrating agents, such as cornstarch, potato starch, or alginic acid, and a lubricant, like stearic acid or magnesium stearate.

The tablets, capsules, and the like can also contain a binder, such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets can be coated with shellac, sugar, or both. A syrup can contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs,

suspensions, syrups, and the like. The percentage of the compound in compositions can, of course, be varied as the amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

Typically in accordance with the present invention, the oral maintenance dose is between about 25 mg and about 50 mg, preferably given once daily. In accordance with the present invention, the preferred unit dosage forms include tablets or capsules.

The active compounds of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they can be enclosed in hard or soft shell capsules, or they can be compressed into tablets, or they can be incorporated directly with the food of the diet.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipients. Such adjuvants, carriers and/or excipients, include, but are not limited to sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable carrier, including adjuvants, excipients or stabilizers. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline,

aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The compounds and/or compositions prepared according to the present invention can be used to treat warm blooded animals, such as mammals, which include humans.

Conventional administration methods may be suitable for use in the present invention.

The present invention relates to a method for treatment of hypertension, congestive heart failure and angina in a mammal in need thereof, which method comprises administering to said mammal an effective amount of carvedilol hydrobromide monohydrate, or solvates thereof, with any of the characteristics noted herein.

The Examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention.

Examples

Example 1

Form 1. Carvedilol HBr Monohydrate.

A suitable reactor is charged with acetone. The acetone solution is sequentially charged with carvedilol, water and 48% aqueous HBr. On addition of the water, the acetone slurry becomes a solution. The reaction mixture is stirred at room temperature. A solid precipitates during the course of the stir. The precipitate is filtered and the collected cake is washed with acetone. The cake is dried under vacuum to a constant weight. The cake is weighed and stored in a polyethylene container.

The single crystal x-ray data for carvedilol hydrobromide monohydrate is provided below.

Table 1. Sample and Crystal Data for Carvedilol Hydrobromide Monohydrate.

Crystallization solvents	Acetone, water	
Crystallization method	Slow cooling	
Empirical formula	$C_{24}H_{29}BrN_2O_5$	
Formula weight	505.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal size	0.18 x 0.14 x 0.08 mm	
Crystal habit	Clear colorless prism	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 18.0356(3) Å	α= 90°
	b = 20.8385(5) Å	β= 103.5680(10)°
	c = 12.9342(3) Å	γ = 90°
Volume	4725.46(18) $Å^3$	
Z	8	
Density (calculated)	1.421 Mg/m^3	
Absorption coefficient	1.777 mm^{-1}	
F(000)	2096	

Table 2. Data collection and structure refinement for Carvedilol Hydrobromide Monohydrate.

Diffractometer	KappaCCD
Radiation source	Fine-focus sealed tube, MoK_α
Data collection method	CCD; rotation images; thick slices
Theta range for data collection	3.42 to 23.27°
Index ranges	$0 \le h \le 20$, $0 \le k \le 23$, $-14 \le l \le 13$
Reflections collected	30823
Independent reflections	3404 [R(int) = 0.042]
Coverage of independent reflections	99.7 %
Variation in check reflections	N/A
Absorption correction	Symmetry-related measurements
Max. and min. transmission	0.8709 and 0.7404
Structure solution technique	Direct methods
Structure solution program	SHELXTL V5.10 UNIX (Bruker, 1997)
Refinement technique	Full-matrix least-squares on F^2
Refinement program	SHELXTL V5.10 UNIX (Bruker, 1997)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3404 / 11 / 336
Goodness-of-fit on F^2	1.020
Δ/σ_{max}	0.000
Final R indices	
3071 data; $I>2\sigma(I)$	R1 = 0.0353, wR2 = 0.0797
all data	R1 = 0.0405, wR2 = 0.0829
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + [(0.0304P)^2 + 14.1564P]$ where $P = [MAX(F_o^2, 0) + 2F_c^2]/3$
Largest diff. peak and hole	0.786 and -0.914 e.Å^{-3}

Refinement summary:	
Ordered Non-H atoms, XYZ	Freely refined
Ordered Non-H atoms, U	Anisotropic
H atoms (on carbon), XYZ	Idealized positions riding on attached atom
H atoms (on carbon), U	Appropriate constant times Ueq of attached atom
H atoms (on heteroatoms), XYZ	Freely refined
H atoms (on heteroatoms), U	Refined Isotropically
Disordered atoms, OCC	See Table 10
Disordered atoms, XYZ	Refined with distance restaints
Disordered atoms, U	Anisotropic

Table 3. Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters ($Å^2$) for Carvedilol Hydrobromide Monohydrate.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Br1	0.5000	0.22079(2)	-0.2500	0.04329(15)
Br2	0.0000	0.40821(2)	-0.2500	0.04510(16)
O1	0.19543(10)	0.37037(10)	-0.00168(15)	0.0328(5)
O2	0.08660(19)	0.48508(15)	0.1085(2)	0.0312(7)
O2'	0.0825(3)	0.4816(3)	-0.0328(4)	0.0311(13)
O3	-0.19428(10)	0.39492(10)	-0.01310(15)	0.0347(5)
O4	-0.24723(12)	0.46974(11)	0.11008(16)	0.0404(5)
O99A	-0.0880(5)	0.4236(3)	0.1967(7)	0.0430(19)
O99B	-0.0833(5)	0.4514(4)	0.1784(7)	0.0431(19)
N1	0.34092(16)	0.25072(13)	-0.1793(2)	0.0390(7)
N2	-0.03151(14)	0.39706(13)	-0.0026(2)	0.0314(6)
C1	0.26859(15)	0.35551(14)	-0.0070(2)	0.0301(7)
C2	0.33380(16)	0.38188(15)	0.0568(2)	0.0339(7)
C3	0.40553(17)	0.36537(16)	0.0409(3)	0.0402(8)
C4	0.41433(17)	0.32249(16)	-0.0364(3)	0.0401(8)
C5	0.34850(16)	0.29538(15)	-0.0986(2)	0.0343(7)
C6	0.26499(17)	0.23737(14)	-0.2202(2)	0.0343(7)
C7	0.23145(19)	0.19604(15)	-0.3022(2)	0.0401(8)
C8	0.15313(19)	0.19096(15)	-0.3275(2)	0.0412(8)
C9	0.10866(18)	0.22594(14)	-0.2721(2)	0.0364(7)
C10	0.14185(17)	0.26731(14)	-0.1910(2)	0.0323(7)
C11	0.22085(16)	0.27356(13)	-0.1639(2)	0.0300(7)
C12	0.27490(16)	0.31103(13)	-0.0855(2)	0.0294(6)
C13	0.18523(16)	0.41746(14)	0.0740(2)	0.0301(7)
C14	0.10181(16)	0.43671(13)	0.0452(2)	0.0305(7)
C15	0.05016(15)	0.37919(14)	0.0363(2)	0.0289(6)
C16	-0.08143(16)	0.33991(14)	-0.0272(2)	0.0361(7)
C17	-0.16200(16)	0.35626(16)	-0.0833(2)	0.0380(7)
C18	-0.27156(15)	0.40680(14)	-0.0445(2)	0.0300(6)
C19	-0.30049(16)	0.44705(14)	0.0236(2)	0.0316(7)
C20	-0.37754(18)	0.46060(16)	0.0007(3)	0.0409(8)
C21	-0.42545(18)	0.43467(17)	-0.0895(3)	0.0499(9)
C22	-0.39733(18)	0.39593(17)	-0.1567(3)	0.0504(9)
C23	-0.31949(17)	0.38199(15)	-0.1342(3)	0.0388(7)
C24	-0.2743(2)	0.50999(17)	0.1833(3)	0.0482(9)

Table 4. Selected Bond Lengths (Å) for Carvedilol Hydrobromide Monohydrate.

O1-C1	1.373(3)	O1-C13	1.428(3)
O2-C14	1.366(4)	O2'-C14	1.360(6)
O3-C18	1.380(3)	O3-C17	1.435(3)
O4-C19	1.376(4)	O4-C24	1.433(4)
N1-C6	1.376(4)	N1-C5	1.381(4)
N2-C16	1.482(4)	N2-C15	1.488(4)
C1-C2	1.382(4)	C1-C12	1.399(4)
C2-C3	1.399(4)	C3-C4	1.378(5)
C4-C5	1.388(4)	C5-C12	1.415(4)
C6-C7	1.389(4)	C6-C11	1.416(4)
C7-C8	1.377(5)	C8-C9	1.399(4)
C9-C10	1.381(4)	C10-C11	1.391(4)
C11-C12	1.458(4)	C13-C14	1.517(4)
C14-C15	1.506(4)	C16-C17	1.503(4)
C18-C23	1.374(4)	C18-C19	1.403(4)
C19-C20	1.380(4)	C20-C21	1.388(5)
C21-C22	1.368(5)	C22-C23	1.396(4)

Table 5. Selected bond angles (°) for Carvedilol Hydrobromide Monohydrate.

C1-O1-C13	118.0(2)	C18-O3-C17	116.5(2)
C19-O4-C24	117.2(2)	C6-N1-C5	109.9(3)
C16-N2-C15	112.0(2)	O1-C1-C2	125.0(3)
O1-C1-C12	115.4(2)	C2-C1-C12	119.6(3)
C1-C2-C3	120.1(3)	C4-C3-C2	122.3(3)
C3-C4-C5	117.1(3)	N1-C5-C4	129.2(3)
N1-C5-C12	108.5(3)	C4-C5-C12	122.4(3)
N1-C6-C7	129.4(3)	N1-C6-C11	108.9(3)
C7-C6-C11	121.7(3)	C8-C7-C6	117.9(3)
C7-C8-C9	121.1(3)	C10-C9-C8	121.0(3)
C9-C10-C11	119.1(3)	C10-C11-C6	119.1(3)
C10-C11-C12	134.7(3)	C6-C11-C12	106.2(3)
C1-C12-C5	118.6(3)	C1-C12-C11	134.8(3)
C5-C12-C11	106.6(3)	O1-C13-C14	107.0(2)
O2'-C14-O2	83.4(3)	O2'-C14-C15	116.4(3)
O2-C14-C15	115.2(3)	O2'-C14-C13	115.6(3)
O2-C14-C13	112.0(3)	C15-C14-C13	111.6(2)
N2-C15-C14	111.8(2)	N2-C16-C17	113.0(3)
O3-C17-C16	108.1(2)	C23-C18-O3	125.0(3)
C23-C18-C19	120.1(3)	O3-C18-C19	114.9(2)
O4-C19-C20	125.4(3)	O4-C19-C18	115.1(2)
C20-C19-C18	119.4(3)	C19-C20-C21	119.8(3)
C22-C21-C20	120.9(3)	C21-C22-C23	119.7(3)
C18-C23-C22	120.0(3)		

Table 6. Hydrogen Bonds and Short C-H···X Contacts for Carvedilol Hydrobromide Monohydrate (Å and °).

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1-H1N···Br1	0.76(3)	2.53(4)	3.269(3)	166(3)
N2-H2NA···O99A	0.83(4)	2.29(4)	3.037(10)	149(3)
N2-H2NA···O99B	0.83(4)	2.13(4)	2.943(10)	165(4)
N2-H2NB···O2#1	0.89(5)	2.17(4)	2.873(4)	135(4)
O2'-H2O'···Br2	0.67(5)	2.65(7)	3.237(6)	149(12)
O99A-H99A···Br1#2	0.94(3)	2.49(4)	3.395(8)	163(6)
O99B-H99B···Br2#1	0.94(3)	2.38(3)	3.320(8)	173(6)
C15-H15A···O1 0.99	2.38	2.783(3)	103.2	
C15-H15B···Br1#2	0.99	2.85	3.738(3)	149.3
C16-H16A···Br1#2	0.99	2.88	3.760(3)	148.2

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y+1,-z #2 -x+1/2,-y+1/2,-z

Table 7. Selected torsion angles (°) for Carvedilol Hydrobromide Monohydrate.

C13-O1-C1-C2	1.2(4)	C13-O1-C1-C12	-177.5(2)
O1-C1-C2-C3	-177.0(3)	C12-C1-C2-C3	1.7(4)
C1-C2-C3-C4	-0.8(5)	C2-C3-C4-C5	-0.5(5)
C6-N1-C5-C4	-179.7(3)	C6-N1-C5-C12	0.8(3)
C3-C4-C5-N1	-178.6(3)	C3-C4-C5-C12	0.8(4)
C5-N1-C6-C7	179.4(3)	C5-N1-C6-C11	-0.9(3)
N1-C6-C7-C8	179.5(3)	C11-C6-C7-C8	-0.1(4)
C6-C7-C8-C9	-0.4(5)	C7-C8-C9-C10	0.8(5)
C8-C9-C10-C11	-0.6(4)	C9-C10-C11-C6	0.0(4)
C9-C10-C11-C12	-179.9(3)	N1-C6-C11-C10	-179.4(3)
C7-C6-C11-C10	0.3(4)	N1-C6-C11-C12	0.6(3)
C7-C6-C11-C12	-179.7(3)	O1-C1-C12-C5	177.4(2)
C2-C1-C12-C5	-1.4(4)	O1-C1-C12-C11	-2.4(5)
C2-C1-C12-C11	178.8(3)	N1-C5-C12-C1	179.6(2)
C4-C5-C12-C1	0.1(4)	N1-C5-C12-C11	-0.5(3)
C4-C5-C12-C11	180.0(3)	C10-C11-C12-C1	-0.3(6)
C6-C11-C12-C1	179.8(3)	C10-C11-C12-C5	179.9(3)
C6-C11-C12-C5	-0.1(3)	C1-O1-C13-C14	166.1(2)
O1-C13-C14-O2'	-82.6(4)	O1-C13-C14-O2	-175.8(2)
O1-C13-C14-C15	53.4(3)	C16-N2-C15-C14	171.3(2)
O2'-C14-C15-N2	-38.6(4)	O2-C14-C15-N2	56.6(3)
C13-C14-C15-N2	-174.2(2)	C15-N2-C16-C17	-170.5(2)
C18-O3-C17-C16	-170.7(2)	N2-C16-C17-O3	-63.3(3)
C17-O3-C18-C23	3.3(4)	C17-O3-C18-C19	-177.3(3)
C24-O4-C19-C20	1.0(4)	C24-O4-C19-C18	-178.7(3)
C23-C18-C19-O4	-179.2(3)	O3-C18-C19-O4	1.4(4)
C23-C18-C19-C20	1.0(4)	O3-C18-C19-C20	-178.3(3)
O4-C19-C20-C21	179.9(3)	C18-C19-C20-C21	-0.4(5)
C19-C20-C21-C22	-0.3(5)	C20-C21-C22-C23	0.3(6)
O3-C18-C23-C22	178.2(3)	C19-C18-C23-C22	-1.1(5)
C21-C22-C23-C18	0.4(5)		

Table 8. Anisotropic Atomic Displacement Parameters ($Å^2$) for Carvedilol Hydrobromide Monohydrate.

The anisotropic atomic displacement factor exponent takes the form:

$$-2\pi^2 [h^2a^{*2}U_{11} + ... + 2hka^* b^* U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	0.0484(3)	0.0447(3)	0.0464(3)	0.000	0.0306(2)	0.000
Br2	0.0707(3)	0.0413(3)	0.0234(2)	0.000	0.0111(2)	0.000
O1	0.0272(11)	0.0408(12)	0.0323(11)	0.0067(9)	0.0108(9)	-0.0009(9)
O2	0.0416(18)	0.0306(18)	0.0215(17)	-0.0006(14)	0.0077(15)	0.0059(14)
O2'	0.038(3)	0.028(3)	0.031(3)	0.001(3)	0.014(3)	0.000(3)
O3	0.0254(11)	0.0473(13)	0.0308(11)	-0.0091(9)	0.0058(9)	-0.0001(9)
O4	0.0400(12)	0.0500(14)	0.0323(11)	-0.0076(10)	0.0108(10)	0.0019(10)
O99A	0.042(3)	0.044(5)	0.040(4)	-0.004(4)	0.004(3)	0.002(4)
O99B	0.033(3)	0.061(6)	0.035(4)	-0.004(4)	0.007(2)	-0.010(4)
N1	0.0384(17)	0.0449(17)	0.0393(16)	0.0053(13)	0.0203(14)	0.0112(13)
N2	0.0270(13)	0.0341(15)	0.0332(15)	0.0015(13)	0.0075(12)	0.0033(11)
C1	0.0283(16)	0.0324(16)	0.0321(16)	0.0078(13)	0.0124(13)	0.0005(12)
C2	0.0321(17)	0.0381(17)	0.0327(16)	0.0056(13)	0.0100(13)	-0.0014(13)
C3	0.0301(17)	0.048(2)	0.0412(18)	0.0104(16)	0.0051(14)	-0.0044(14)
C4	0.0290(17)	0.0471(19)	0.0470(19)	0.0133(16)	0.0148(15)	0.0064(14)
C5	0.0324(17)	0.0390(17)	0.0343(16)	0.0113(14)	0.0132(14)	0.0065(14)
C6	0.0391(18)	0.0334(17)	0.0339(17)	0.0099(14)	0.0161(14)	0.0088(14)
C7	0.056(2)	0.0324(17)	0.0362(18)	0.0011(14)	0.0204(16)	0.0098(15)
C8	0.055(2)	0.0337(18)	0.0357(18)	-0.0020(14)	0.0119(16)	0.0003(15)
C9	0.0411(18)	0.0344(17)	0.0348(17)	0.0030(14)	0.0111(14)	-0.0009(14)
C10	0.0362(17)	0.0321(16)	0.0323(16)	0.0038(13)	0.0155(14)	0.0022(13)
C11	0.0377(17)	0.0275(15)	0.0277(15)	0.0079(12)	0.0136(13)	0.0040(13)
C12	0.0305(16)	0.0309(16)	0.0295(15)	0.0085(13)	0.0122(13)	0.0017(12)
C13	0.0311(16)	0.0331(16)	0.0265(15)	-0.0019(12)	0.0078(12)	-0.0021(12)
C14	0.0325(16)	0.0307(16)	0.0290(16)	0.0010(13)	0.0083(13)	0.0015(13)
C15	0.0263(15)	0.0327(16)	0.0289(15)	0.0031(12)	0.0090(12)	0.0043(12)
C16	0.0322(16)	0.0347(17)	0.0390(18)	-0.0078(14)	0.0036(14)	0.0016(13)
C17	0.0298(16)	0.0477(19)	0.0342(17)	-0.0106(15)	0.0031(13)	0.0023(14)
C18	0.0246(15)	0.0317(16)	0.0337(16)	0.0031(13)	0.0069(13)	-0.0014(12)
C19	0.0299(16)	0.0352(17)	0.0313(16)	0.0063(13)	0.0103(13)	-0.0031(13)
C20	0.0379(18)	0.0382(18)	0.051(2)	0.0048(15)	0.0194(16)	0.0033(15)
C21	0.0245(17)	0.050(2)	0.073(3)	0.0038(19)	0.0059(17)	0.0012(15)
C22	0.0326(18)	0.053(2)	0.057(2)	-0.0075(18)	-0.0052(16)	-0.0012(16)
C23	0.0317(17)	0.0407(18)	0.0407(18)	-0.0045(14)	0.0021(14)	-0.0004(14)
C24	0.065(2)	0.050(2)	0.0325(18)	-0.0027(15)	0.0176(17)	0.0098(17)

Table 9. Hydrogen Atom Coordinates and Isotropic Atomic Displacement Parameters ($Å^2$) for Carvedilol Hydrobromide Monohydrate.

	x/a	y/b	z/c	U
H2O	0.086(3)	0.471(3)	0.155(4)	0.047
H2O'	0.082(6)	0.465(5)	-0.077(6)	0.047
H99A	-0.073(4)	0.3802(19)	0.201(6)	0.064
H99B	-0.060(4)	0.490(2)	0.205(6)	0.065
H99	-0.1344(19)	0.4409(13)	0.157(3)	0.065
H1N	0.373(2)	0.2411(16)	-0.205(3)	0.039(10)
H2NA	-0.043(2)	0.4188(18)	0.045(3)	0.058(12)
H2NB	-0.036(2)	0.422(2)	-0.060(4)	0.077(14)
H2A	0.3299	0.4112	0.1114	0.041
H3A	0.4497	0.3844	0.0850	0.048
H4A	0.4633	0.3119	-0.0468	0.048
H7A	0.2616	0.1720	-0.3395	0.048
H8A	0.1289	0.1632	-0.3836	0.049
H9A	0.0548	0.2212	-0.2906	0.044
H10A	0.1112	0.2912	-0.1543	0.039
H13A	0.2180	0.4552	0.0713	0.036
H13B	0.1990	0.3994	0.1468	0.036
H14	0.0925	0.4552	-0.0281	0.037
H14'	0.0943	0.4596	0.1099	0.037
H15A	0.0642	0.3477	-0.0132	0.035
H15B	0.0576	0.3585	0.1069	0.035
H16A	-0.0819	0.3172	0.0400	0.043
H16B	-0.0599	0.3103	-0.0723	0.043
H17A	-0.1625	0.3802	-0.1496	0.046
H17B	-0.1922	0.3165	-0.1021	0.046
H20A	-0.3977	0.4876	0.0466	0.049
H21A	-0.4785	0.4439	-0.1048	0.060
H22A	-0.4306	0.3786	-0.2183	0.060
H23A	-0.2996	0.3553	-0.1809	0.047
H24A	-0.2310	0.5242	0.2397	0.072
H24B	-0.3101	0.4858	0.2148	0.072
H24C	-0.3002	0.5475	0.1455	0.072

Table 10. Site Occupation Factors that Deviate from Unity for Carvedilol Hydrobromide Monohydrate.

Atom	sof	Atom	sof	Atom	sof
Br1	1	Br2	1	O1	1
O2	0.65	H2O	0.65	O2'	0.35
H2O'	0.35	O99A	0.50	H99A	0.50
O99B	0.50	H99B	0.50	H99	1
H14	0.65	H14'	0.35		

Example 2

Form 2. Carvedilol HBr (dioxane solvate)

Form 1 is slurried in dioxane between 0 and 40°C for 2 days. The product is filtered and mildly dried.

Example 3

Form 3. Carvedilol HBr (1-pentanol solvate)

Form 1 is slurried in 1-pentanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 4

Form 4. Carvedilol HBr (2-Methyl-1-Propanol solvate)

Form 1 is slurried in 2-Methyl-1-Propanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 5

Form 5. Carvedilol HBr (trifluoroethanol solvate)

Form 1 is slurried in trifluoroethanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 6

Form 6. Carvedilol HBr (2-propanol solvate)

Form 1 is slurried in 2-propanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 7

Form 7. Carvedilol HBr (n-propanol solvate #1)

Carvedilol free base is dissolved in n-propanol/water (95:5), and stoichiometric hydrobromic acid is added. The solution is cooled, and crystallization ensues. The product is filtered, washed with process solvent, and dried.

Example 8

Form 8. Carvedilol HBr (n-propanol solvate #2)

Carvedilol HBr monohydrate (Form 1) is dissolved in n-propanol at ambient temperature. The n-propanol is slowly evaporated off, giving a white solid.

Example 9

Form 9. Carvedilol HBr (anhydrous and solvent free)

Carvedilol free base is dissolved in a solvent (dichloromethane, isopropyl acetate, and acetonitrile have been used) and anhydrous HBr is added (HBr in acetic acid or gaseous HBr). The solution is cooled, and crystallization ensues. The product is filtered, washed with process solvent, and dried.

Example 10

Form 10. Carvedilol HBr (ethanol solvate)

Carvedilol free base is dissolved in ethanol, and anhydrous HBr is added (HBr in acetic acid). The solution is cooled, and crystallization ensues. The product is filtered, washed with process solvent, and dried.

It is to be understood that the invention is not limited to the embodiments illustrated herein. The right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

The various references to journals, patents, and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound which is crystalline carvedilol hydrobromide monohydrate.

2. The compound according to claim 1 having an x-ray diffraction pattern as substantially shown in Figure 1.

3. The compound according to claim 2 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 6.5 ± 0.2 (2θ), 10.3 ± 0.2 (2θ), 15.7 ± 0.2 (2θ), 16.3 ± 0.2 (2θ), 19.8 ± 0.2 (2θ), 20.1 ± 0.2 (2θ), 21.9 ± 0.2 (2θ), 25.2 ± 0.2 (2θ), and 30.6± 0.2 (2θ).

4. The compound according to claim 1 having an infrared spectrum, which comprises characteristic absorption bands expressed in wave numbers as substantially shown in Figure 6.

5. The compound according to claim 1 having a Raman spectrum, which comprises characteristic peaks as shown in Figure 3.

6. A compound which is carvedilol hydrobromide dioxane solvate.

7. The compound according to claim 6 having an x-ray diffraction pattern as substantially shown in Figure 78.

8. The compound according to claim 7 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 7.7 ± 0.2 (2θ), 8.4 ± 0.2 (2θ), 15.6 ± 0.2 (2θ), 17.0 ± 0.2 (2θ), 18.7 ± 0.2 (2θ), 19.5 ± 0.2 (2θ), 21.4 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 27.9 ± 0.2 (2θ).

9. A compound which is carvedilol hydrobromide 1-pentanol solvate.

10. The compound according to claim 9 having an x-ray diffraction pattern as substantially shown in Figure 79.

11. The compound according to claim 10 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 7.5 ± 0.2 (2θ), 7.8 ± 0.2 (2θ), 15.2 ± 0.2 (2θ), 18.9 ± 0.2 (2θ), 22.1 ± 0.2 (2θ), and 31.4 ± 0.2 (2θ).

12. A compound which is carvedilol hydrobromide 2-methyl-1-propanol solvate.

13. The compound according to claim 12 having an x-ray diffraction pattern as substantially shown in Figure 80.

14. The compound according to claim 13 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 7.8 ± 0.2 (2θ), 8.1 ± 0.2 (2θ), 16.3 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), and 28.5 ± 0.2 (2θ).

15. A compound which is carvedilol hydrobromide trifluoroethanol solvate.

16. The compound according to claim 15 having an x-ray diffraction pattern as substantially shown in Figure 81.

17. The compound according to claim 16 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 7.7 ±

0.2 (2θ), 8.4 ± 0.2 (2θ), 15.6 ± 0.2 (2θ), 16.9 ± 0.2 (2θ), 18.9 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), 23.3 ± 0.2 (2θ), 23.8 ± 0.2 (2θ), and 32.7 ± 0.2 (2θ).

18. A compound which is carvedilol hydrobromide 2-propanol solvate.

19. The compound according to claim 18 having an x-ray diffraction pattern as substantially shown in Figure 82.

20. The compound according to claim 19 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 7.9 ± 0.2 (2θ), 8.3 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.7 ± 0.2 (2θ), 23.2 ± 0.2 (2θ), 23.6 ± 0.2 (2θ), and 32.1 ± 0.2 (2θ).

21. A compound which is carvedilol hydrobromide n-propanol solvate #1.

22. The compound according to claim 21 having an x-ray diffraction pattern as substantially shown in Figure 46.

23. The compound according to claim 22 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 7.9 ± 0.2 (2θ), 8.5 ± 0.2 (2θ), 17.0 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.6 ± 0.2 (2θ), 23.1 ± 0.2 (2θ), 23.6 ± 0.2 (2θ), and 21.2 ± 0.2 (2θ).

24. A compound which is carvedilol hydrobromide n-propanol solvate #2.

25. The compound according to claim 24 having an x-ray diffraction pattern as substantially shown in Figure 54.

26. The compound according to claim 25 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 8.0 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.6 ± 0.2 (2θ), 23.1 ± 0.2 (2θ), 25.9 ± 0.2 (2θ), 27.2 ± 0.2 (2θ), 30.6 ± 0.2 (2θ), and 32.2 ± 0.2 (2θ).

27. A compound which is carvedilol hydrobromide ethanol solvate.

28. The compound according to claim 27 having an x-ray diffraction pattern as substantially shown in Figure 70.

29. The compound according to claim 28 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 8.1 ± 0.2 (2θ), 8.6 ± 0.2 (2θ), 13.2 ± 0.2 (2θ), 17.4 ± 0.2 (2θ), 18.6 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), 23.2 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 27.4 ± 0.2 (2θ).

30. A compound which is carvedilol hydrobromide anhydrous.

31. The compound according to claim 30 having an x-ray diffraction pattern as substantially shown in Figure 62.

32. The compound according to claim 31 having characteristic peaks from 0° degrees 2-theta (2θ) to 35° degrees 2-theta (2θ) at about 6.6 ± 0.2 (2θ), 16.1 ± 0.2 (2θ), 17.3 ± 0.2 (2θ), 21.2 ± 0.2 (2θ), 22.1 ± 0.2 (2θ), 24.1 ± 0.2 (2θ), and 27.9 ± 0.2 (2θ).

33. The compound according to claim 30 having an infrared spectrum, which comprises characteristic absorption bands expressed in wave numbers as substantially shown in Figure 67.

34. The compound according to claim 30 having a Raman spectrum, which comprises characteristic peaks as substantially shown in Figure 64.

35. A pharmaceutical composition, comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

36. A pharmaceutical composition, comprising the compound according to claim 30 and a pharmaceutically acceptable carrier.

37. A method of treating hypertension, congestive heart failure, or angina, which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.

38. A method of treating hypertension, congestive heart failure, or angina, which comprises administering to a subject in need thereof an effective amount of a compound according to claim 30.

39. A method of treating hypertension, congestive heart failure, or angina, which comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition according to claim 35.

40. A method of treating hypertension, congestive heart failure, or angina, which comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition according to claim 36.

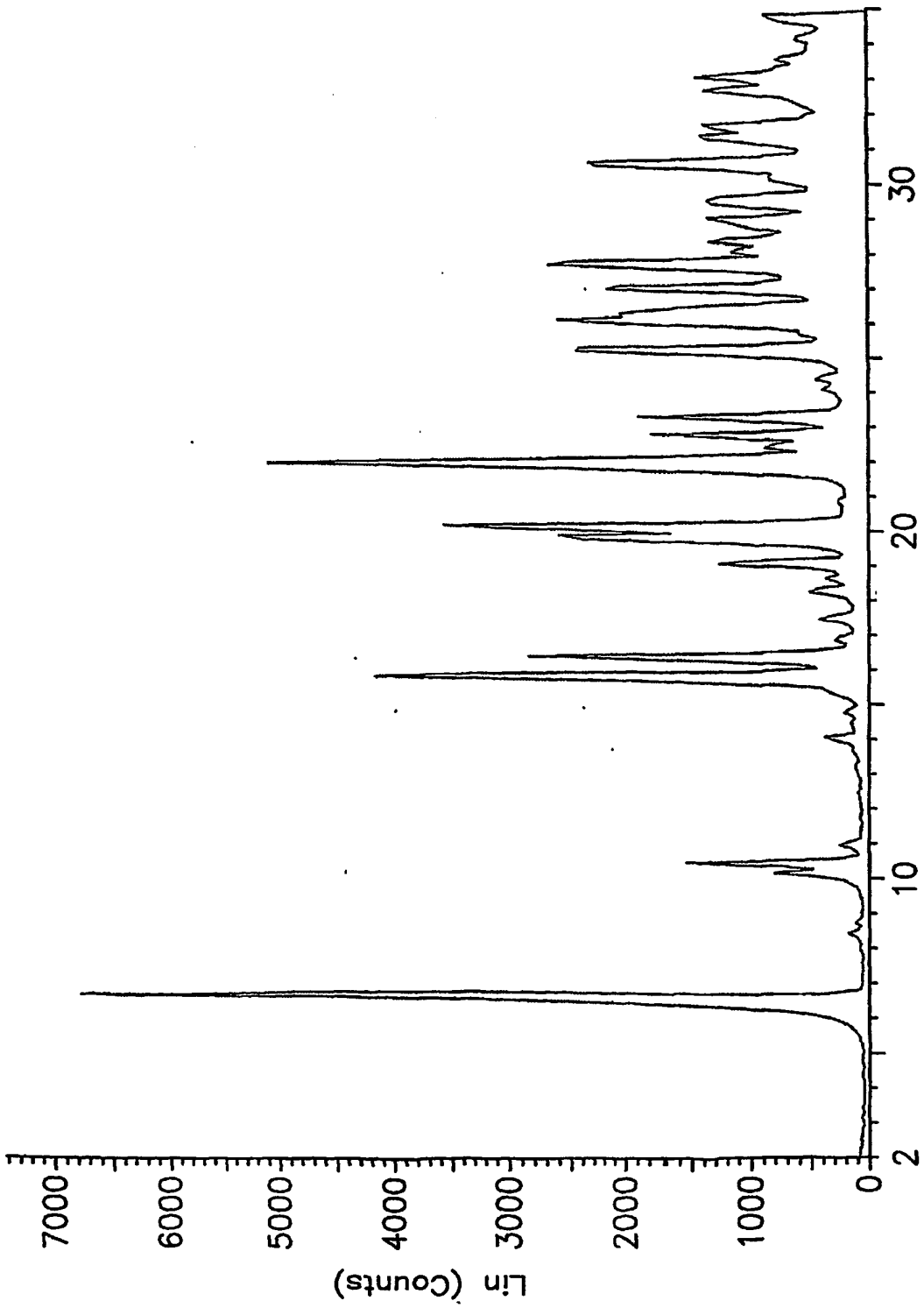

Lin (Counts)
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
2-Theta-Scale

FIG. 1

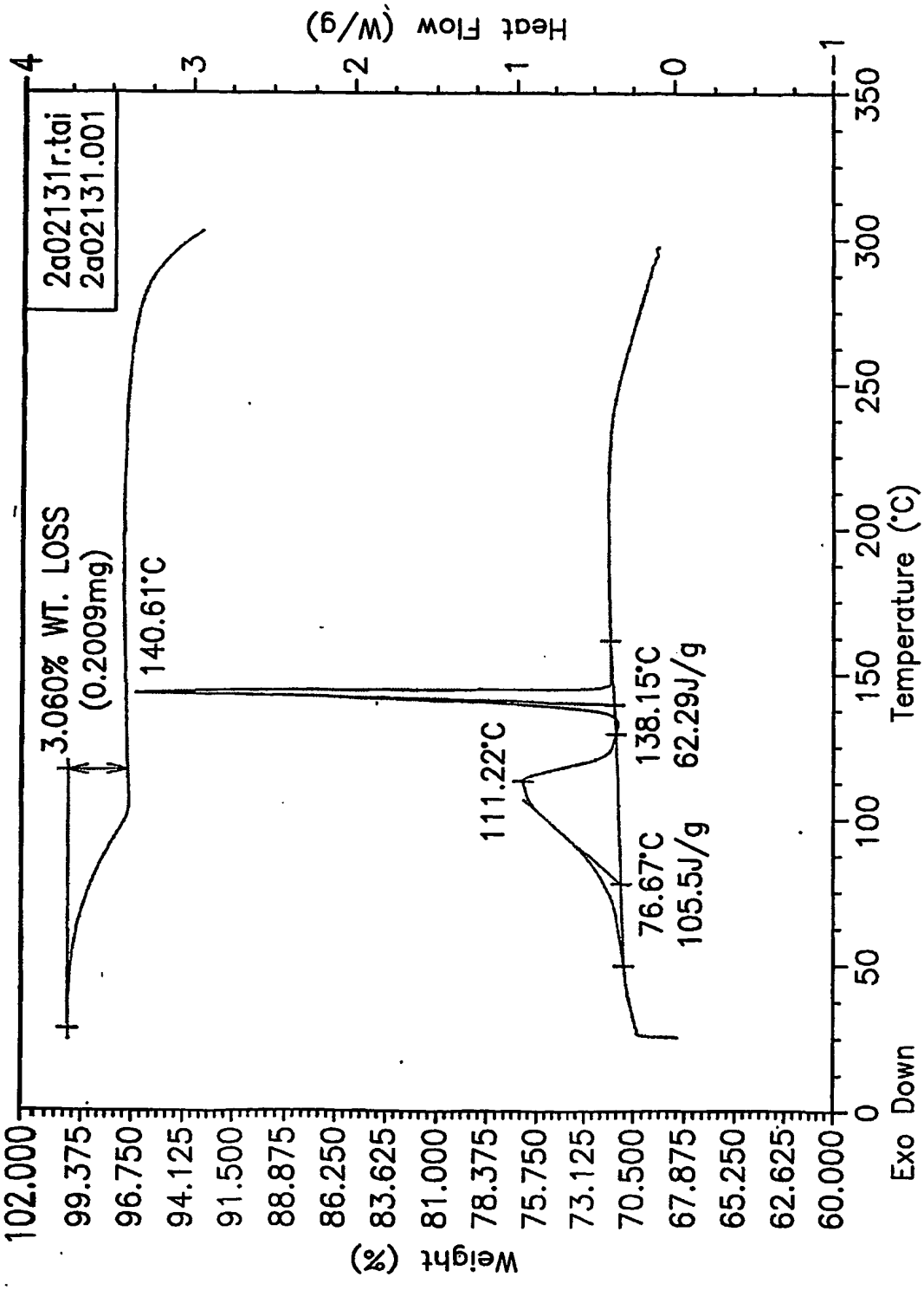


FIG. 2

SUBSTITUTE SHEET (RULE 26)

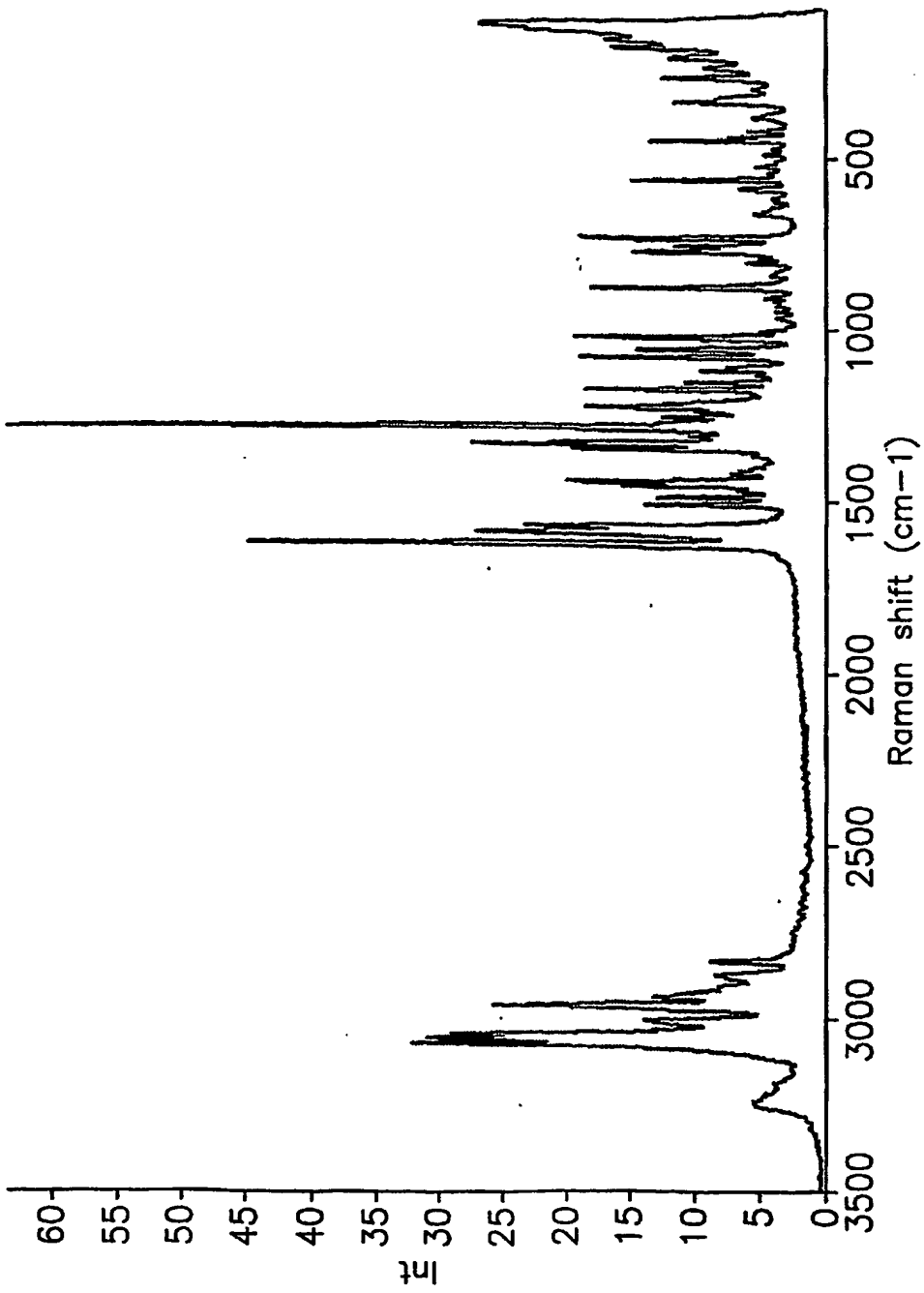

Int
0
5
10
15
20
25
30
35
40
45
50
55
60
3500
3000
2500
2000
1500
1000
500
Raman shift (cm−1)

FIG. 3

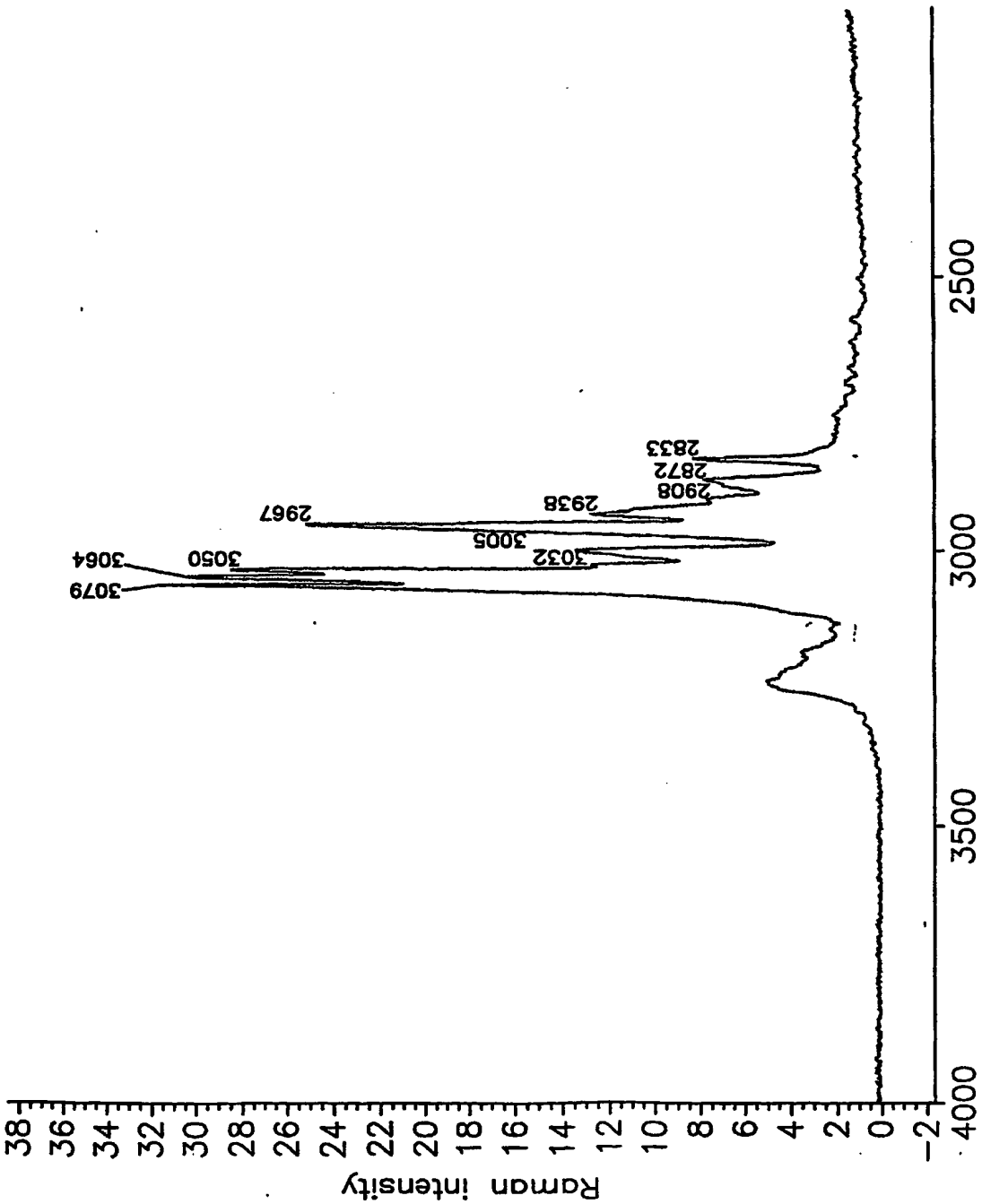

Raman intensity
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
−2
4000
3500
3000
2500
Raman shift (cm−1)
3079
3064
3050
3032
3005
2967
2938
2908
2872
2833

FIG. 4

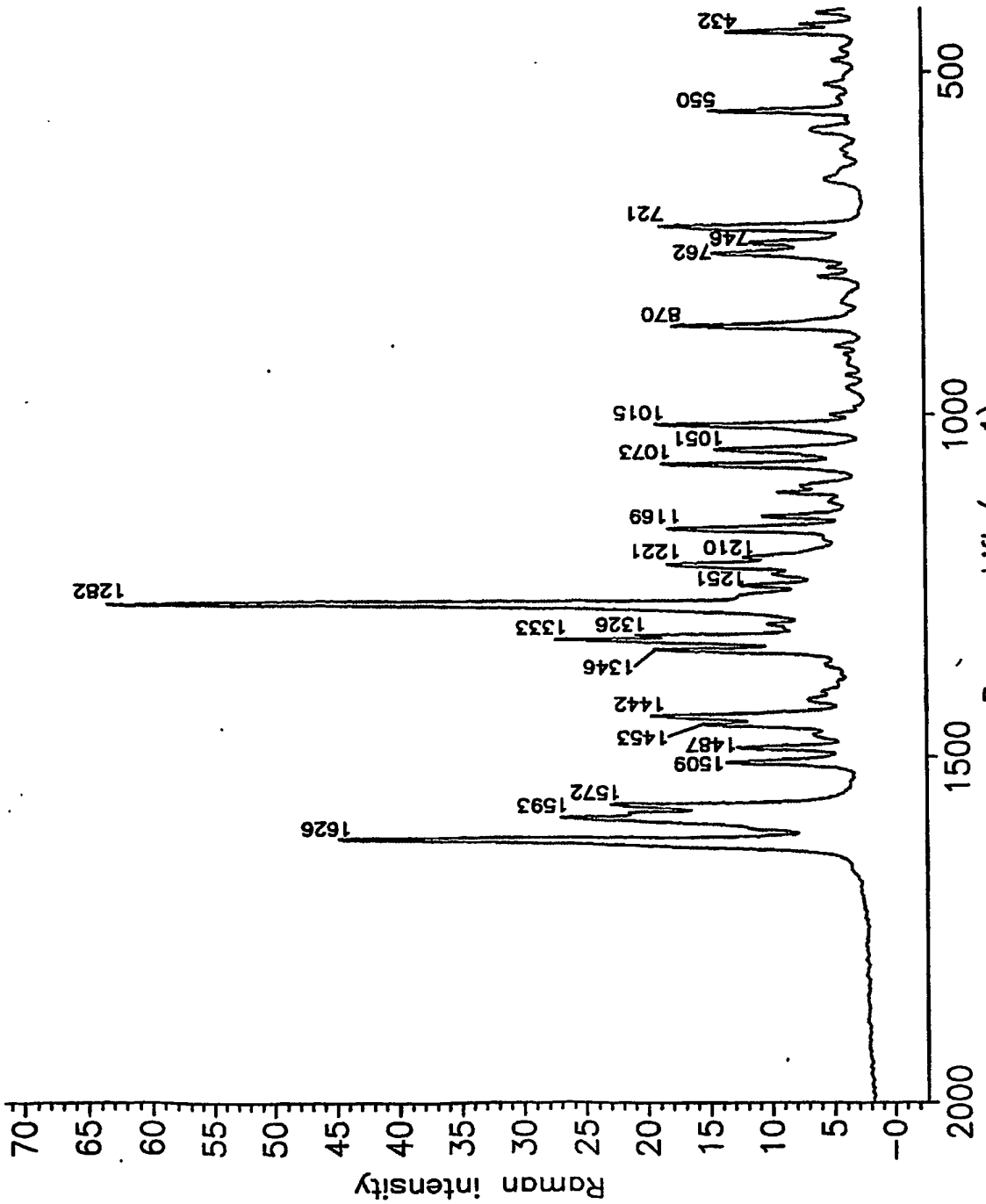

Raman intensity
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
2000
1500
1000
500
Raman shift (cm−1)
1626
1593
1572
1509
1487
1453
1442
1346
1333
1326
1282
1251
1221
1210
1169
1073
1051
1015
870
762
746
721
550
432

FIG. 5

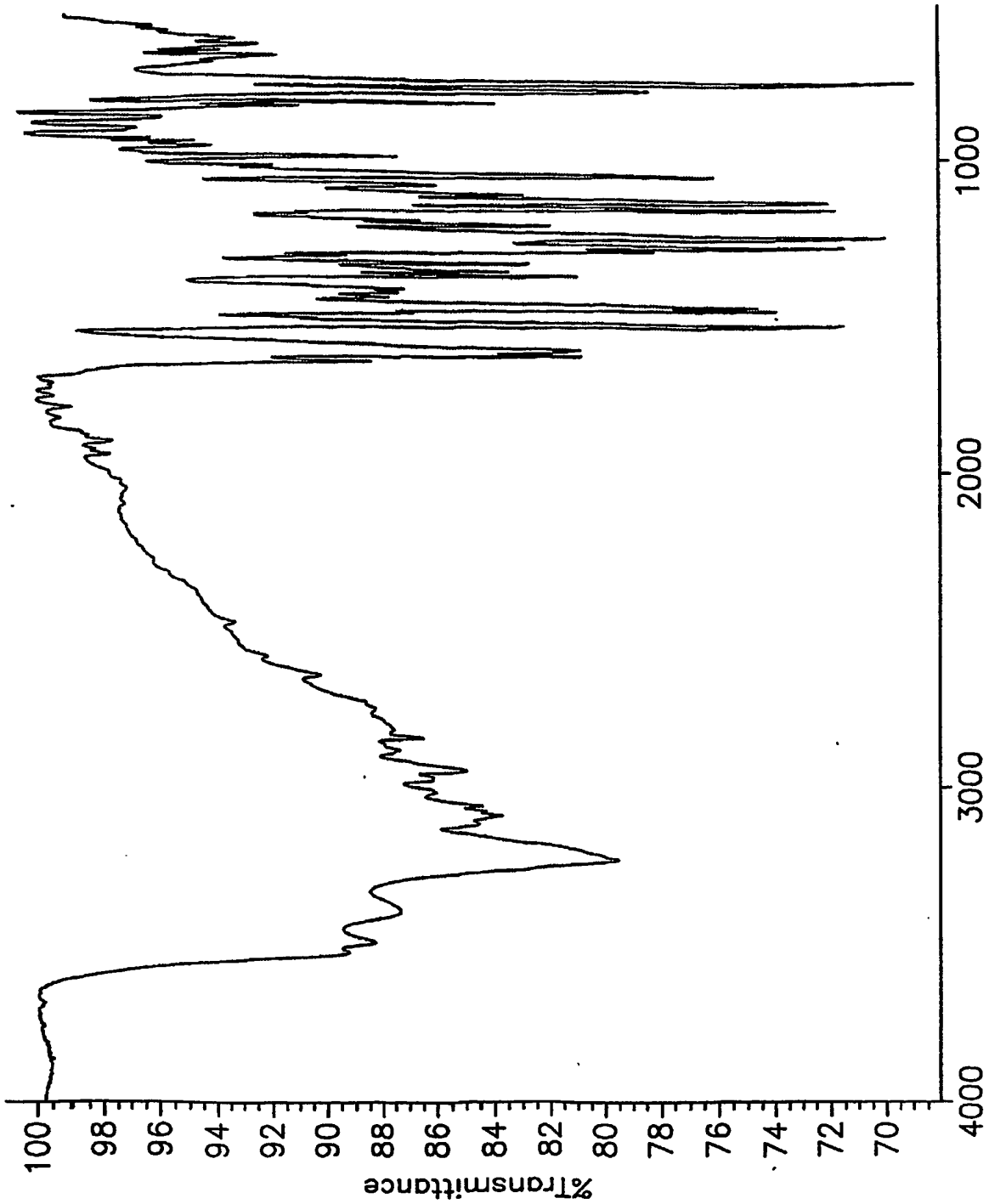

%Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 6

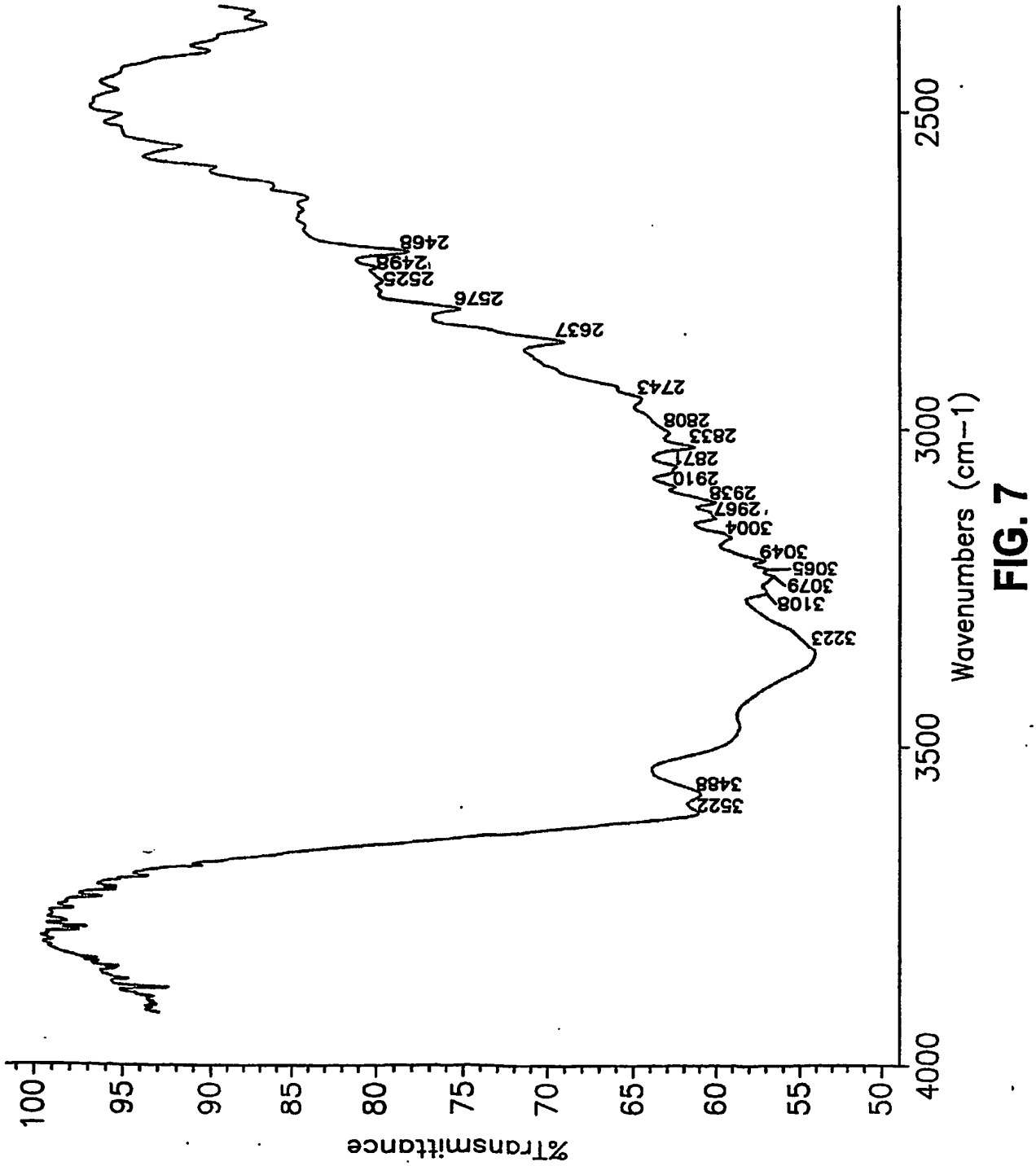

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
4000
3500
3000
2500
Wavenumbers (cm−1)
3522
3488
3223
3108
3079
3065
3049
3004
2967
2938
2910
2871
2833
2808
2743
2637
2576
2525
2498
2468

FIG. 7

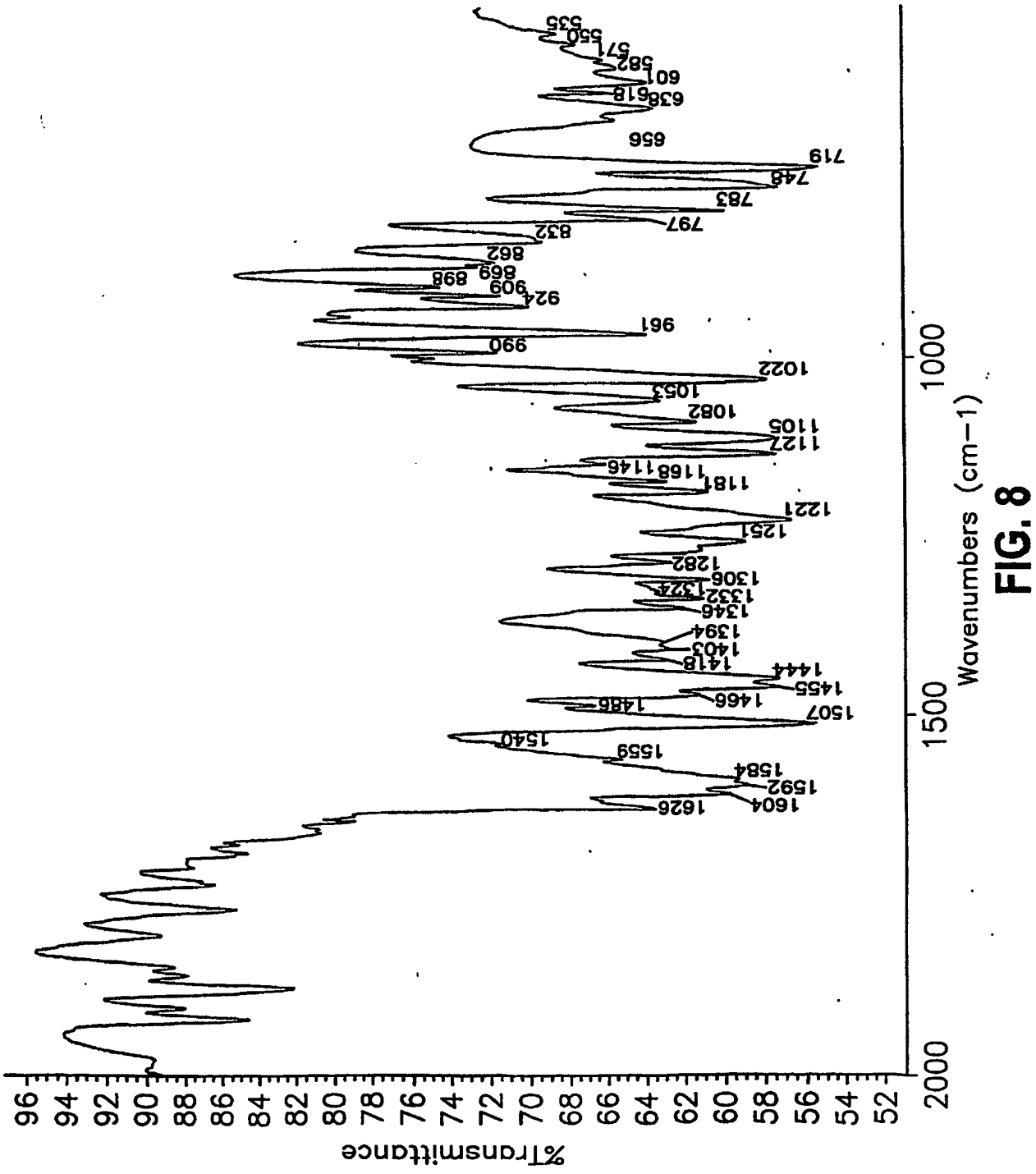

%Transmittance
96 94 92 90 88 86 84 82 80 78 76 74 72 70 68 66 64 62 60 58 56 54 52
2000 1500 1000
Wavenumbers (cm−1)
535 550 571 582 601 618 638 656 719 748 783 797 832 862 869 898 909 924 961 990 1022 1053 1082 1105 1122 1146 1168 1181 1221 1251 1282 1306 1324 1332 1346 1394 1403 1418 1444 1455 1466 1486 1507 1540 1559 1584 1592 1604 1626

FIG. 8

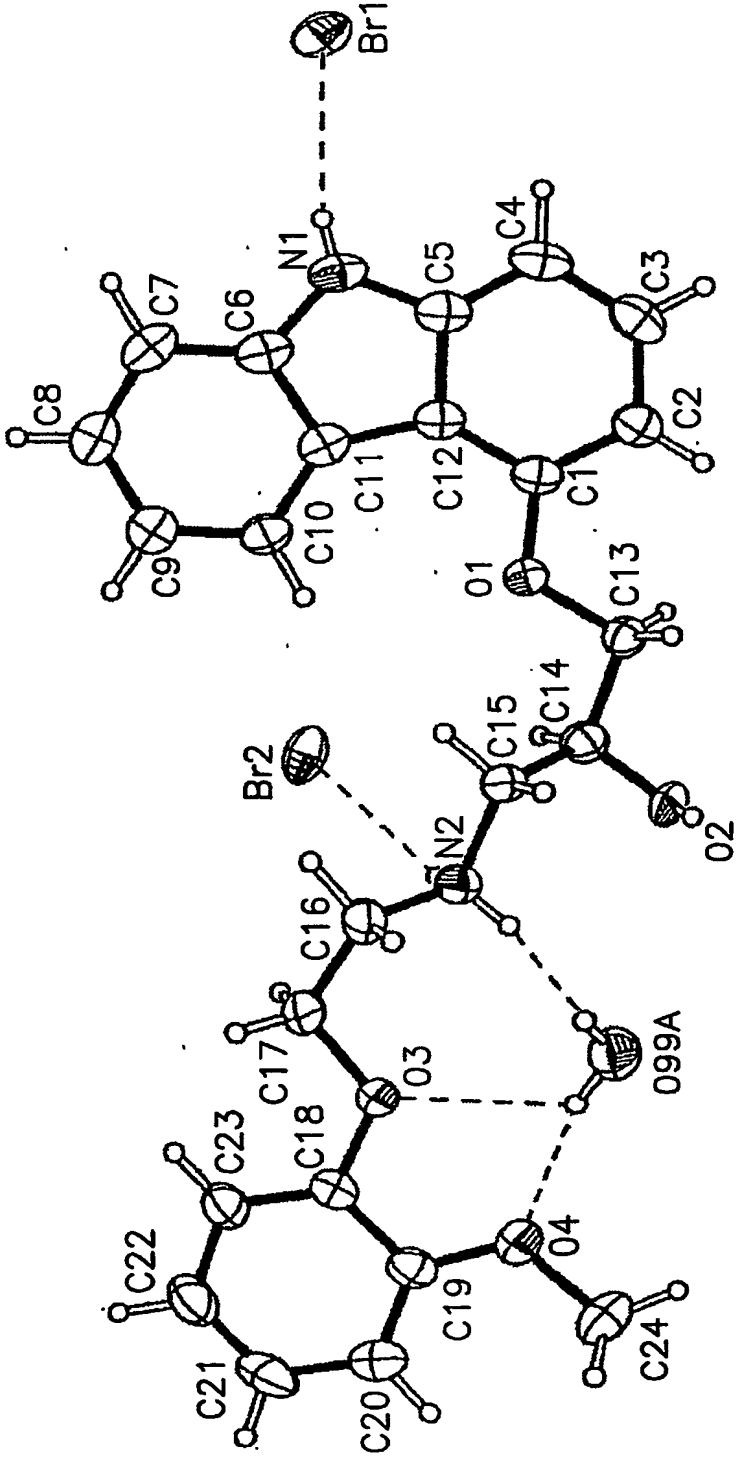

Br1
N1
C4
C5
C3
C7
C6
C8
C2
C11
C12
C1
C10
C9
O1
C13
C14
C15
Br2
N2
O2
C16
C17
O3
O99A
C23
C18
C22
O4
C19
C24
C21
C20

FIG. 9

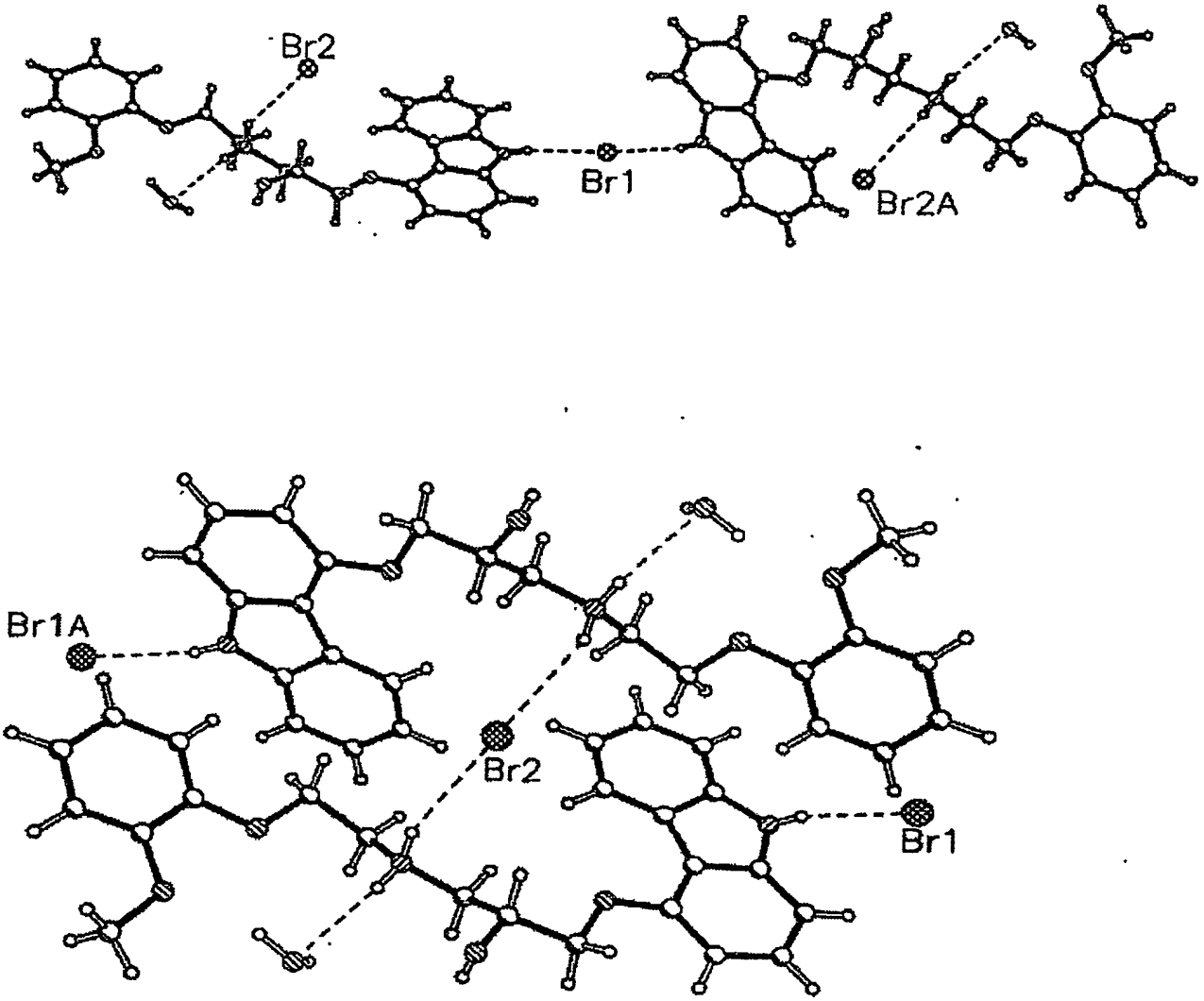


FIG. 10

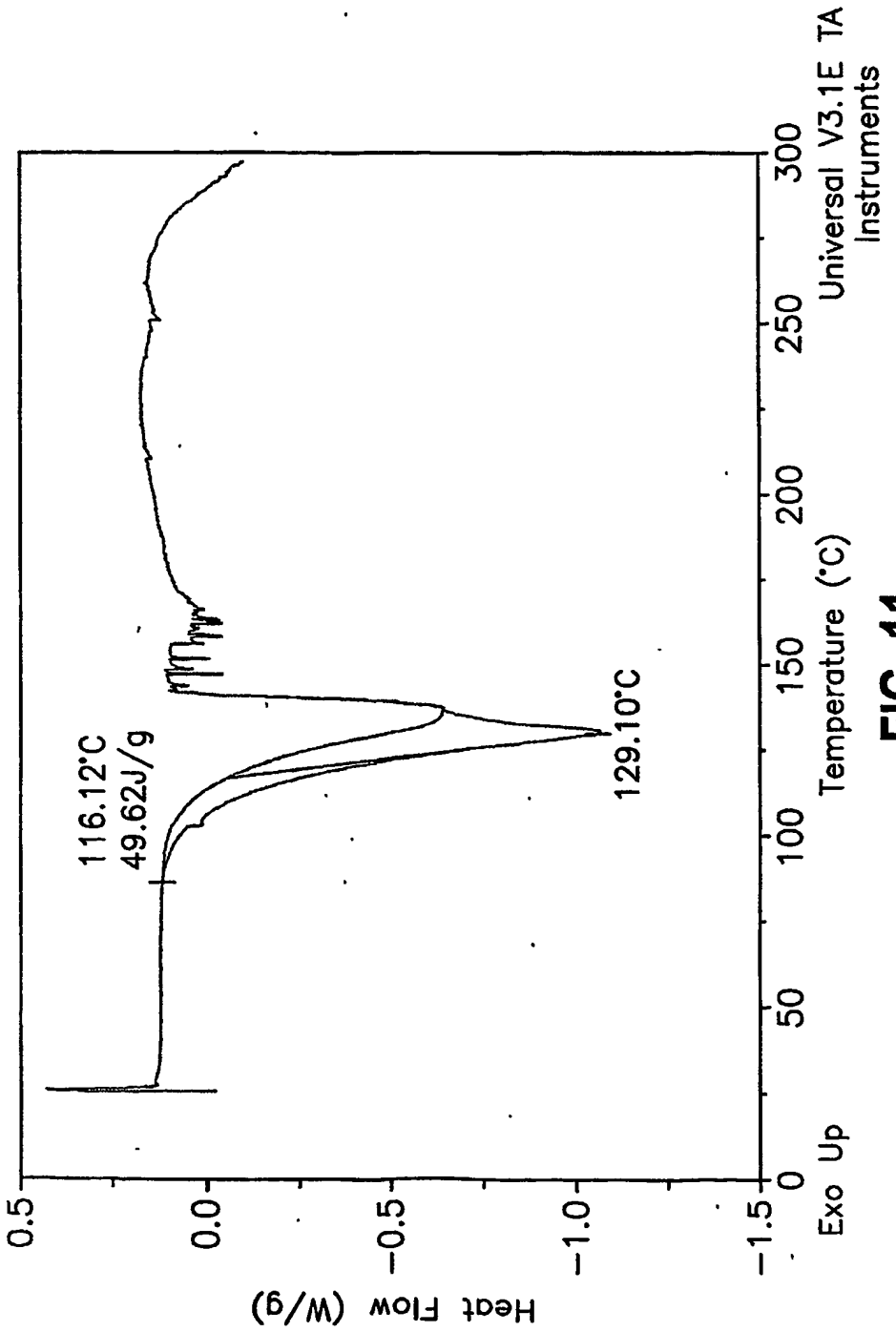

Universal V3.1E TA Instruments
Exo Up
Heat Flow (W/g)
0.5
0.0
−0.5
−1.0
−1.5
0
50
100
150
200
250
300
Temperature (°C)
116.12°C
49.62J/g
129.10°C

FIG. 11

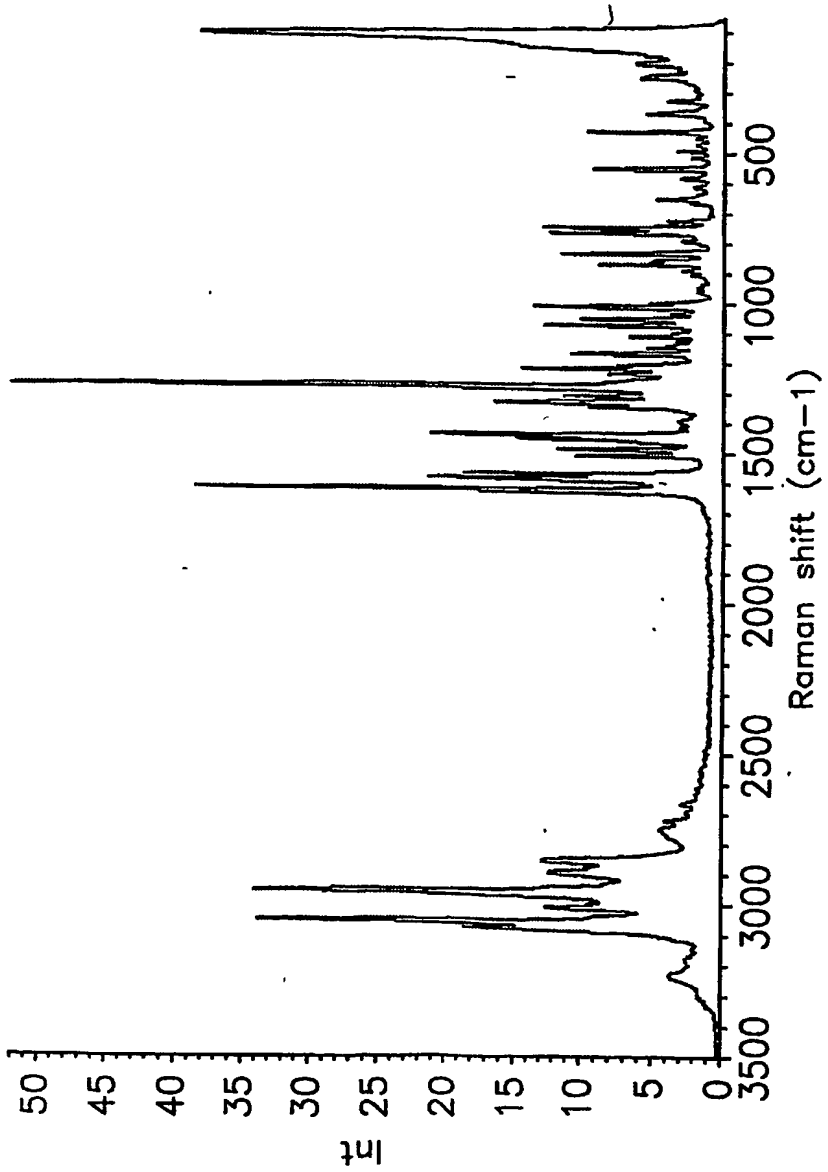

Int
50
45
40
35
30
25
20
15
10
5
0
3500
3000
2500
2000
1500
1000
500
Raman shift (cm−1)

FIG. 12

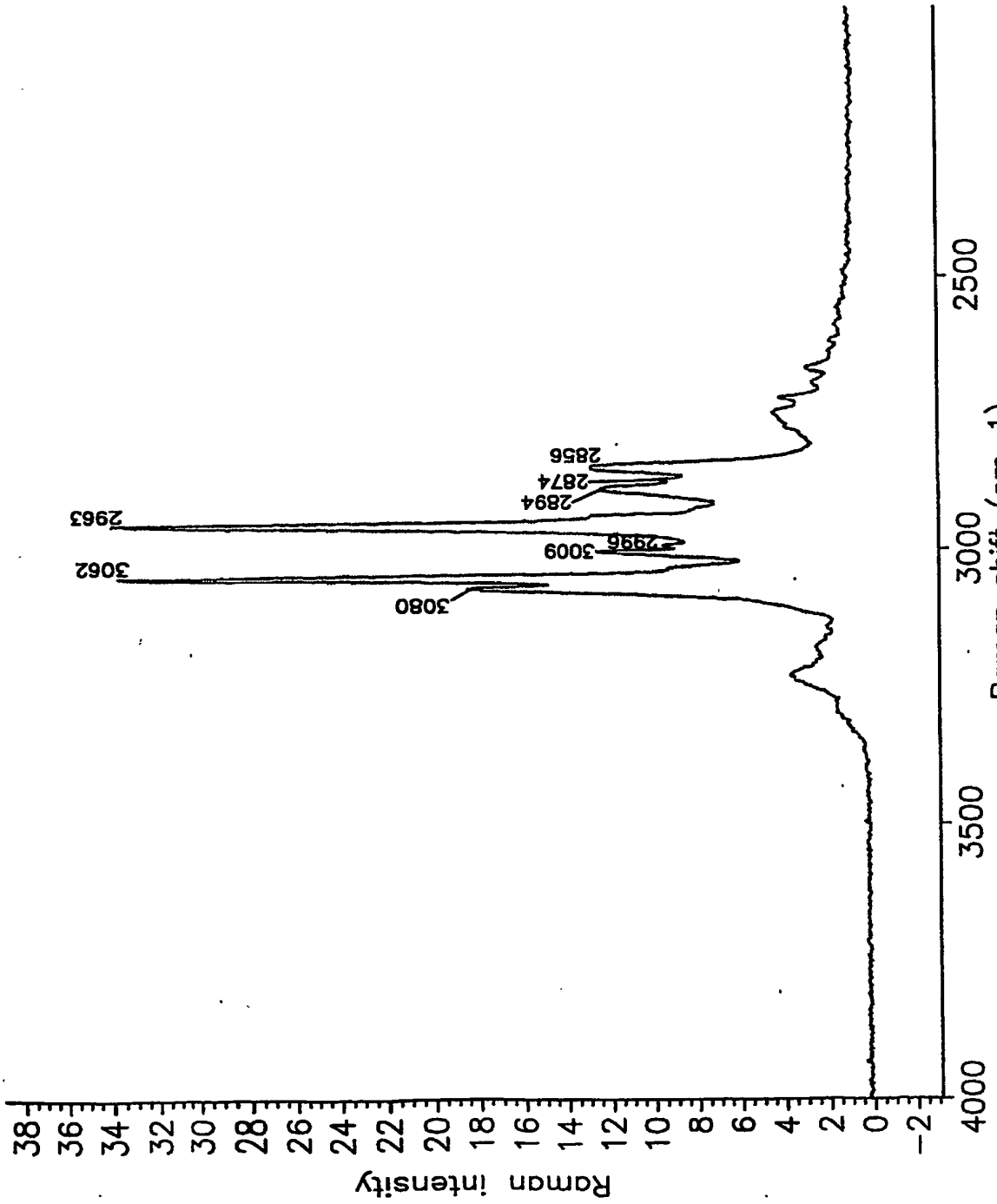

Raman intensity
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
−2
4000
3500
3000
2500
Raman shift (cm−1)
3080
3062
2996
3009
2963
2894
2874
2856

FIG. 13

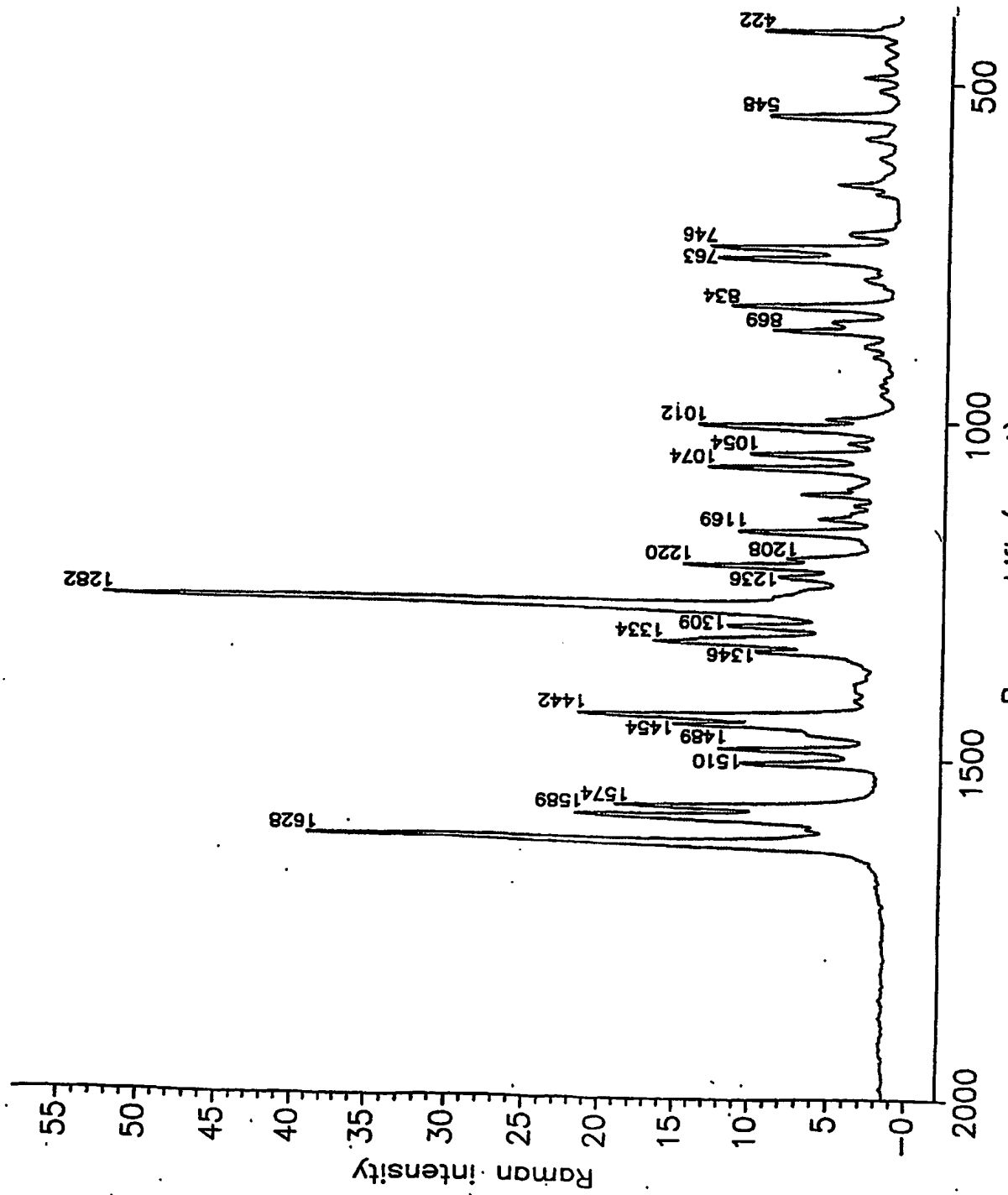

Raman intensity
55
50
45
40
35
30
25
20
15
10
5
0
2000
1500
1000
500
Raman shift (cm−1)
422
548
746
763
834
869
1012
1054
1074
1169
1208
1220
1236
1282
1309
1334
1346
1442
1454
1489
1510
1574
1589
1628

FIG. 14

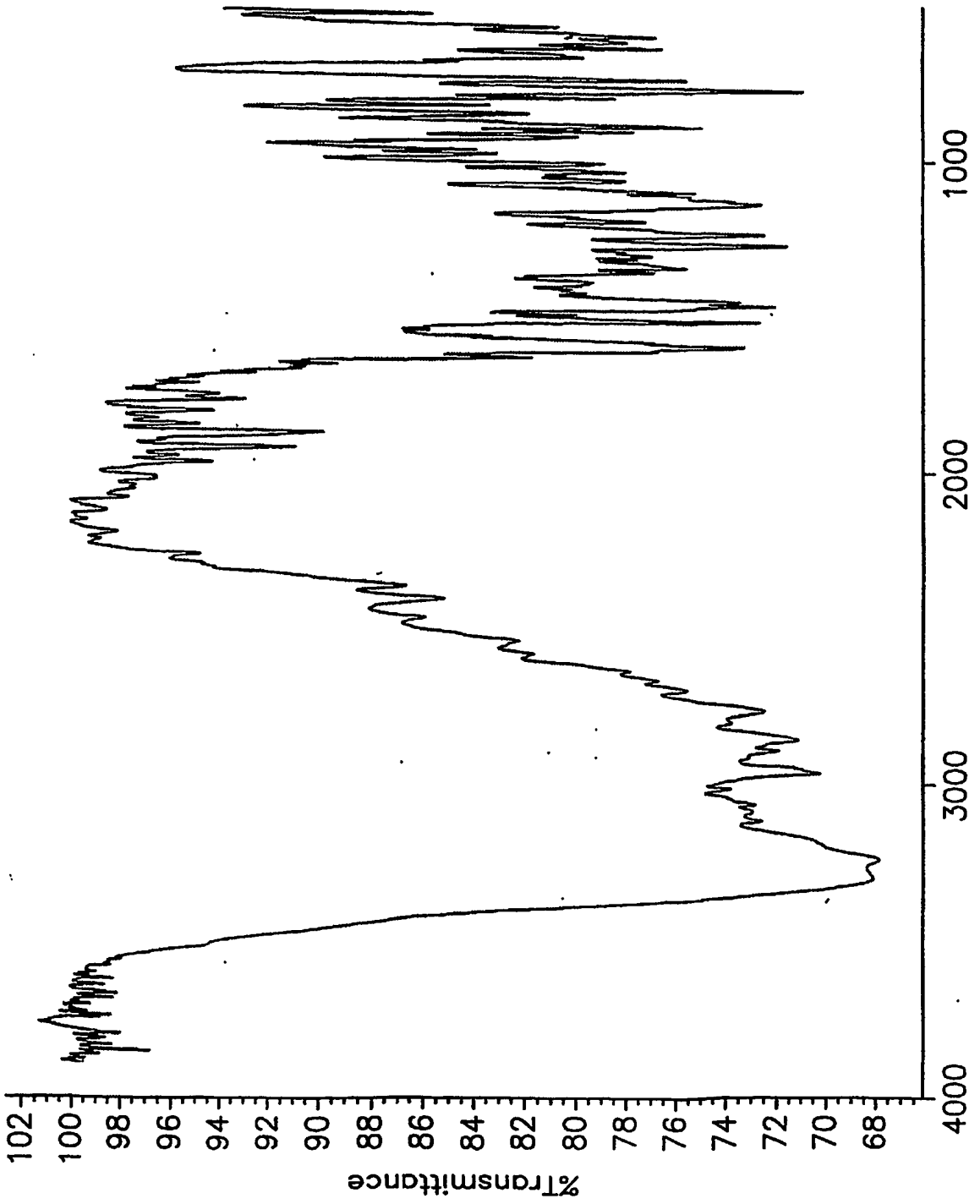

%Transmittance
102
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 15

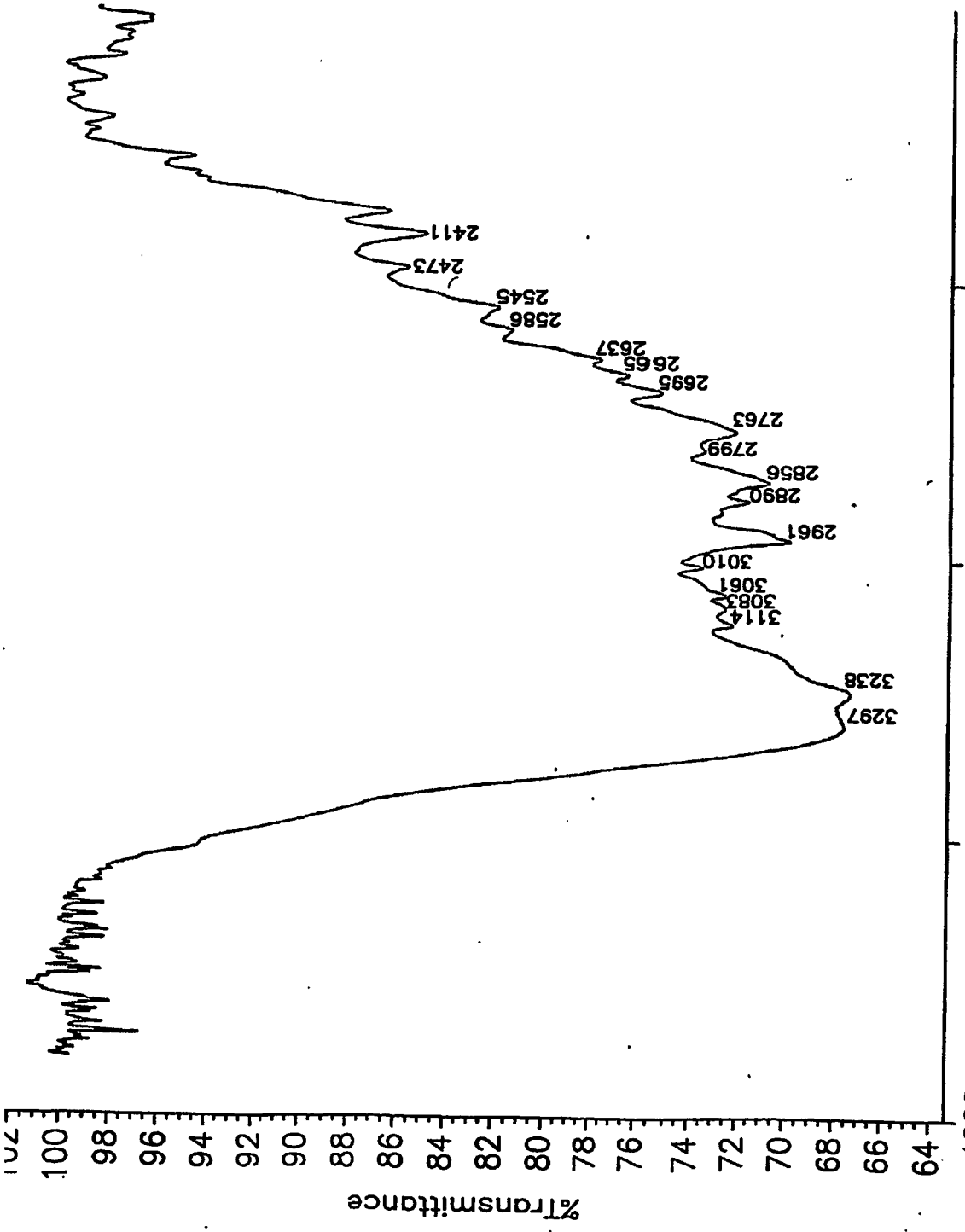

%Transmittance
Wavenumbers (cm−1)
4000
3500
3000
2500
3297
3238
3114
3083
3061
3010
2961
2890
2856
2799
2763
2695
2665
2637
2586
2545
2473
2411

FIG. 16

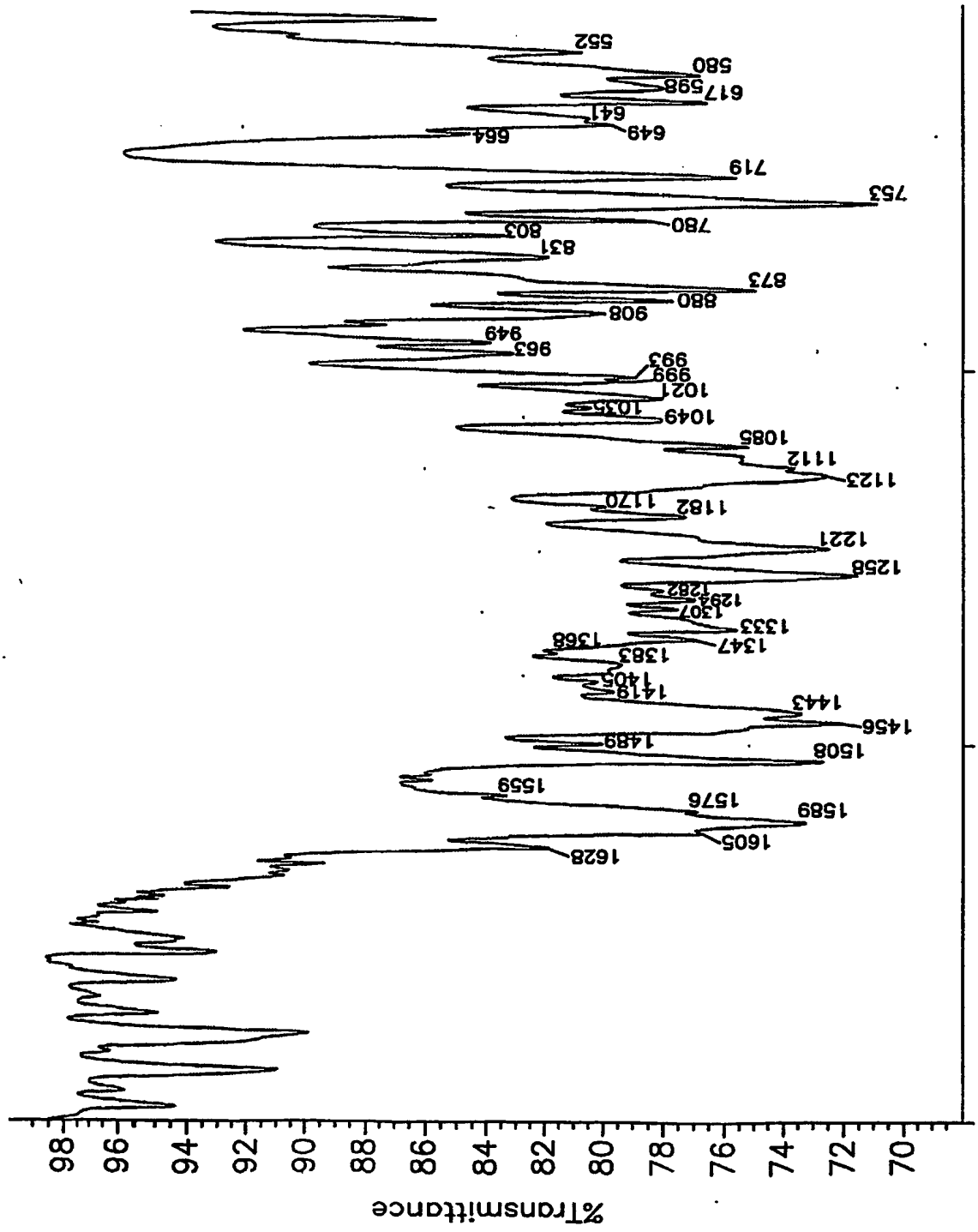

%Transmittance
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
2000
1500
1000
Wavenumbers (cm−1)
552
580
598
617
641
649
664
719
753
780
803
831
873
880
908
949
963
993
999
1021
1035
1049
1085
1112
1123
1170
1182
1221
1258
1282
1293
1307
1333
1347
1368
1383
1405
1419
1443
1456
1489
1508
1559
1576
1589
1605
1628

FIG. 17

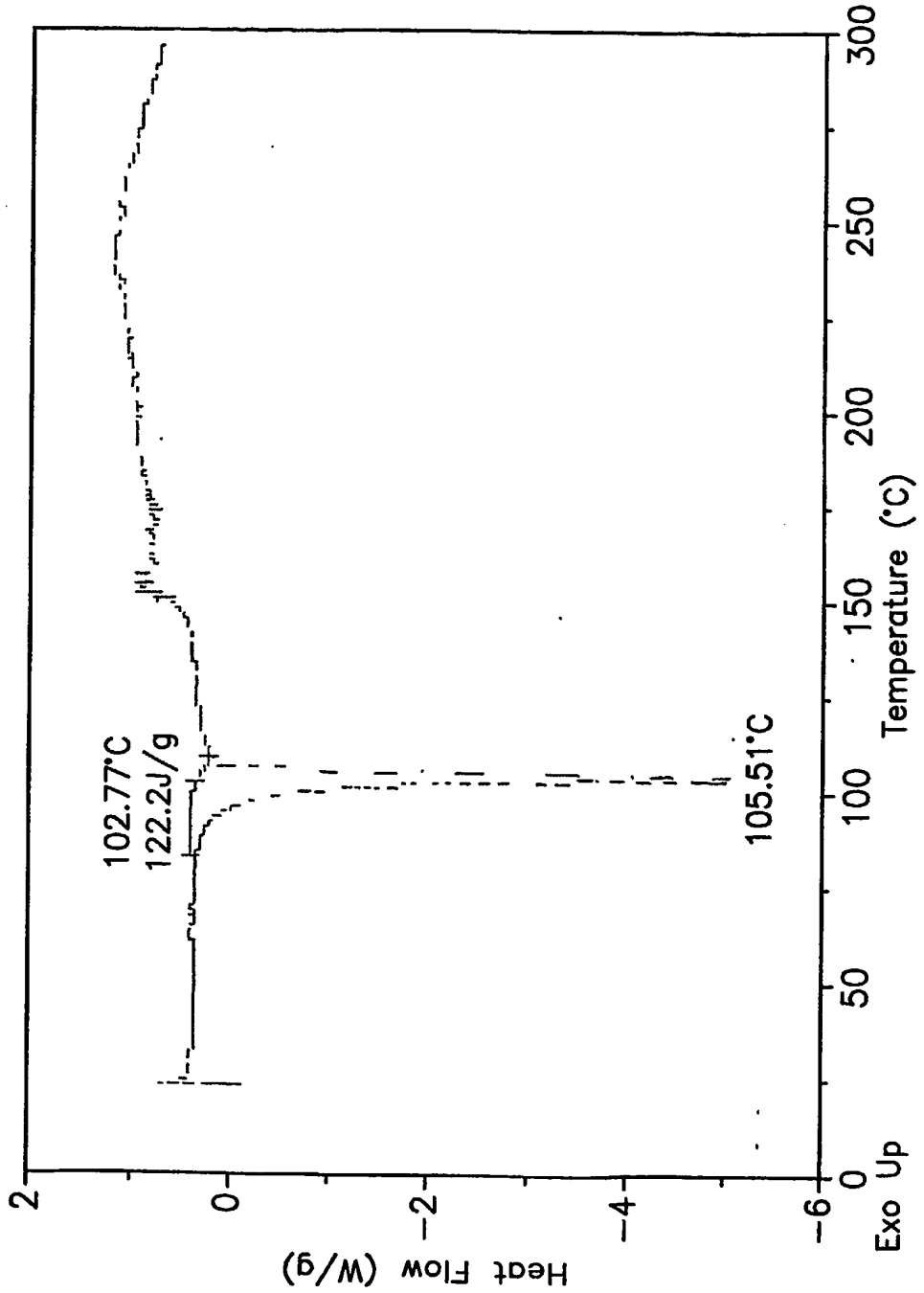

Heat Flow (W/g)
2
0
-2
-4
-6
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
102.77°C
122.2J/g
105.51°C

FIG. 18

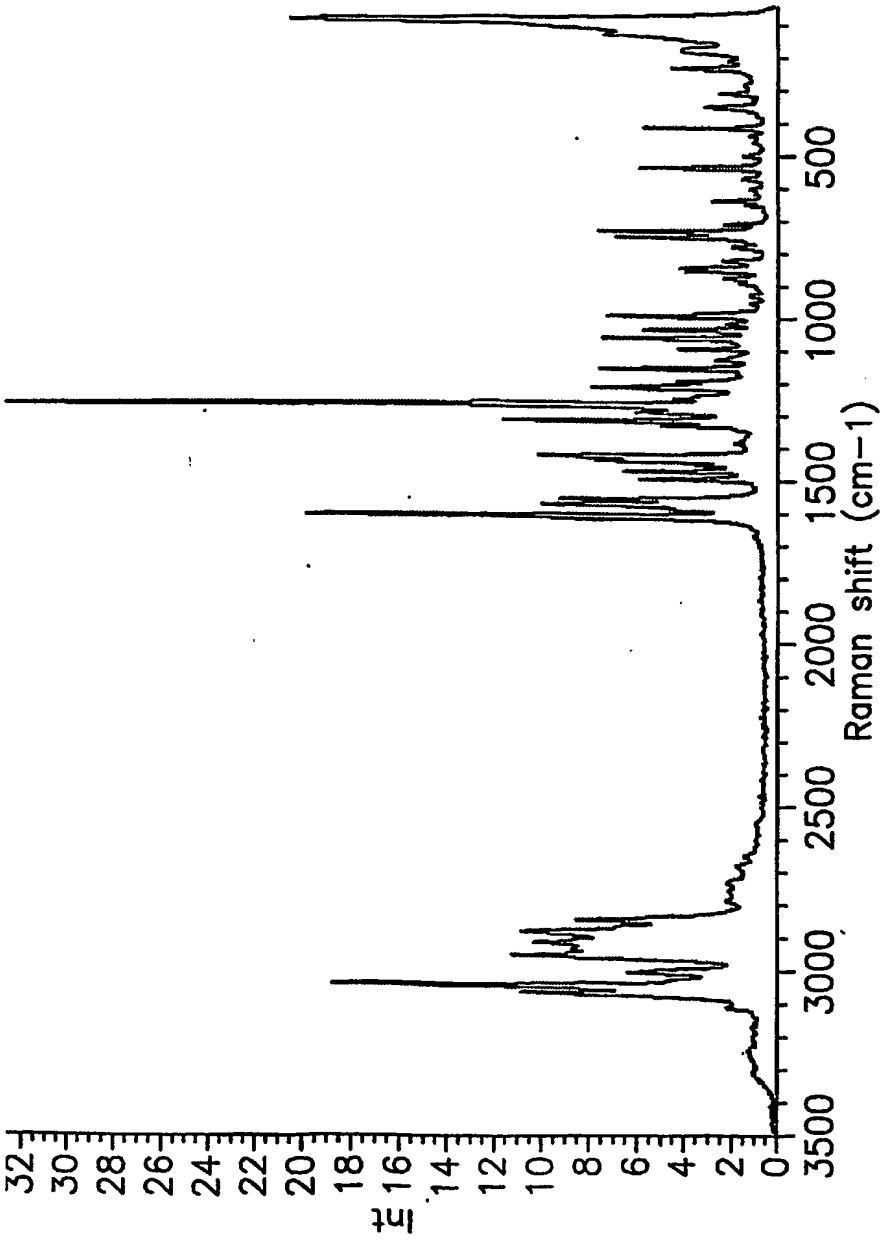

Int
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
3500
3000
2500
2000
1500
1000
500
Raman shift (cm−1)

FIG. 19

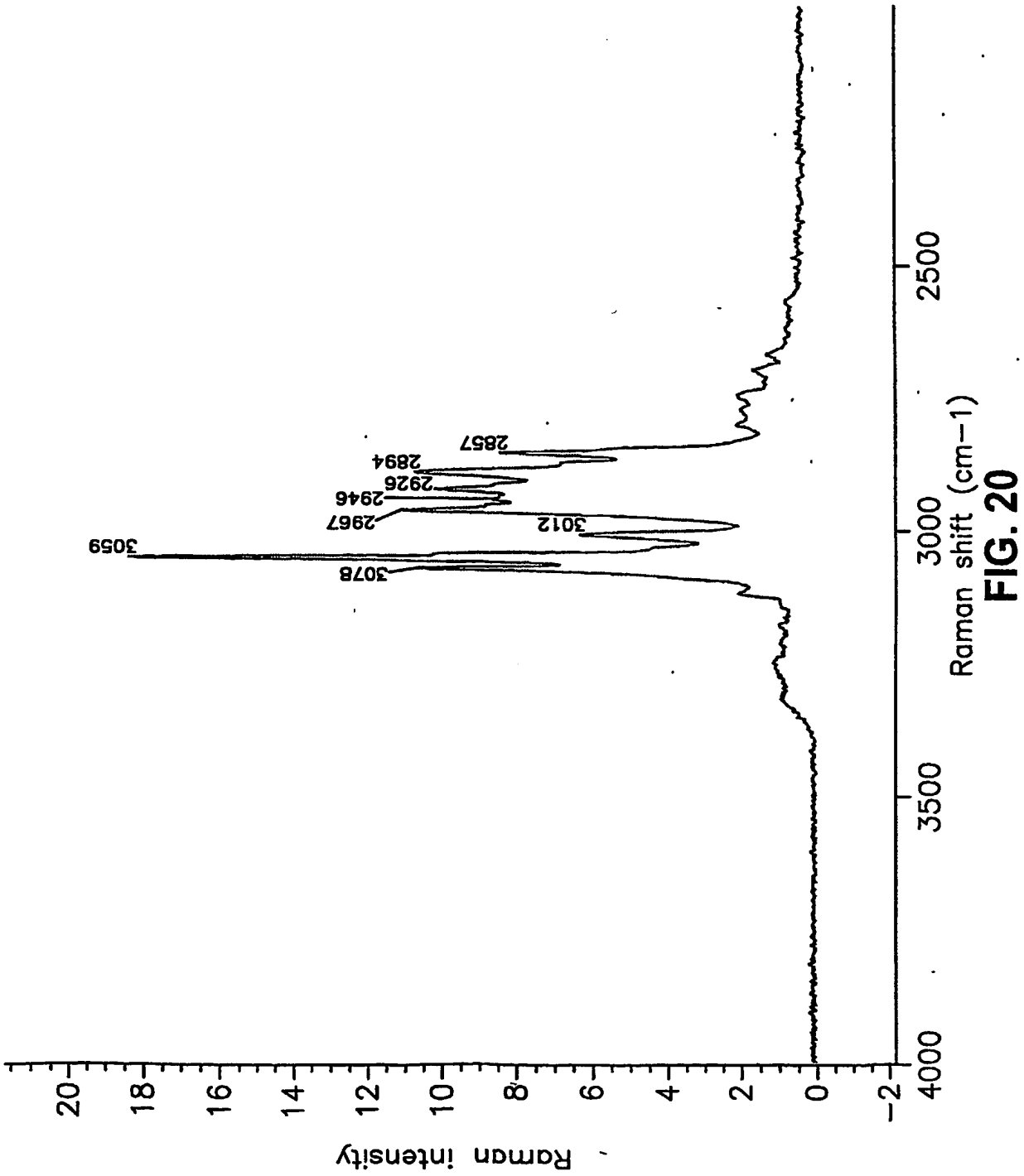

Raman intensity
20
18
16
14
12
10
8
6
4
2
0
-2
4000
3500
3000
2500
Raman shift (cm-1)
3059
3078
3012
2967
2946
2926
2894
2857

FIG. 20

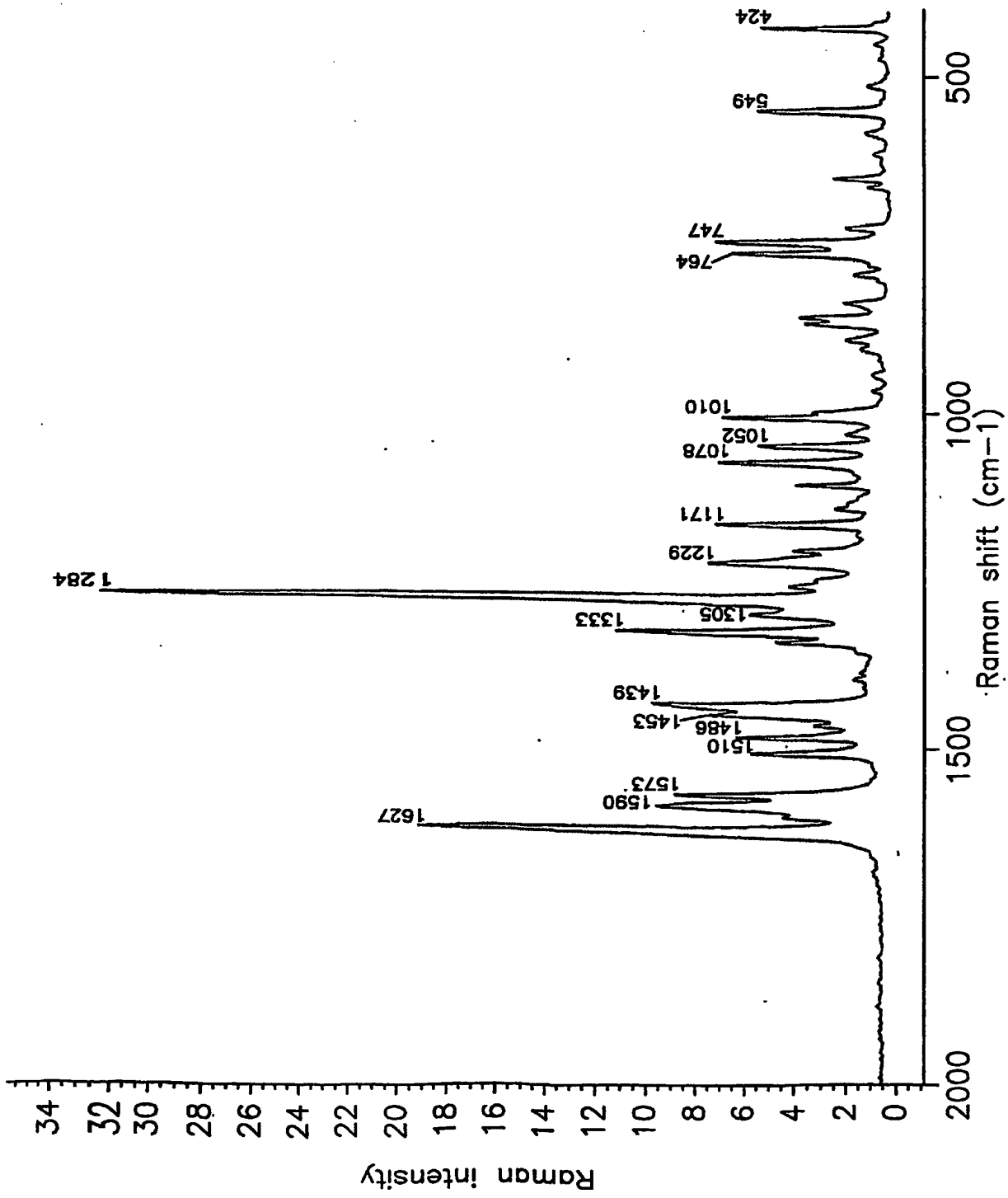

Raman intensity
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
2000
1500
1000
500
Raman shift (cm−1)
1627
1590
1573
1510
1486
1453
1439
1333
1305
1284
1229
1171
1078
1052
1010
764
747
549
424

FIG. 21

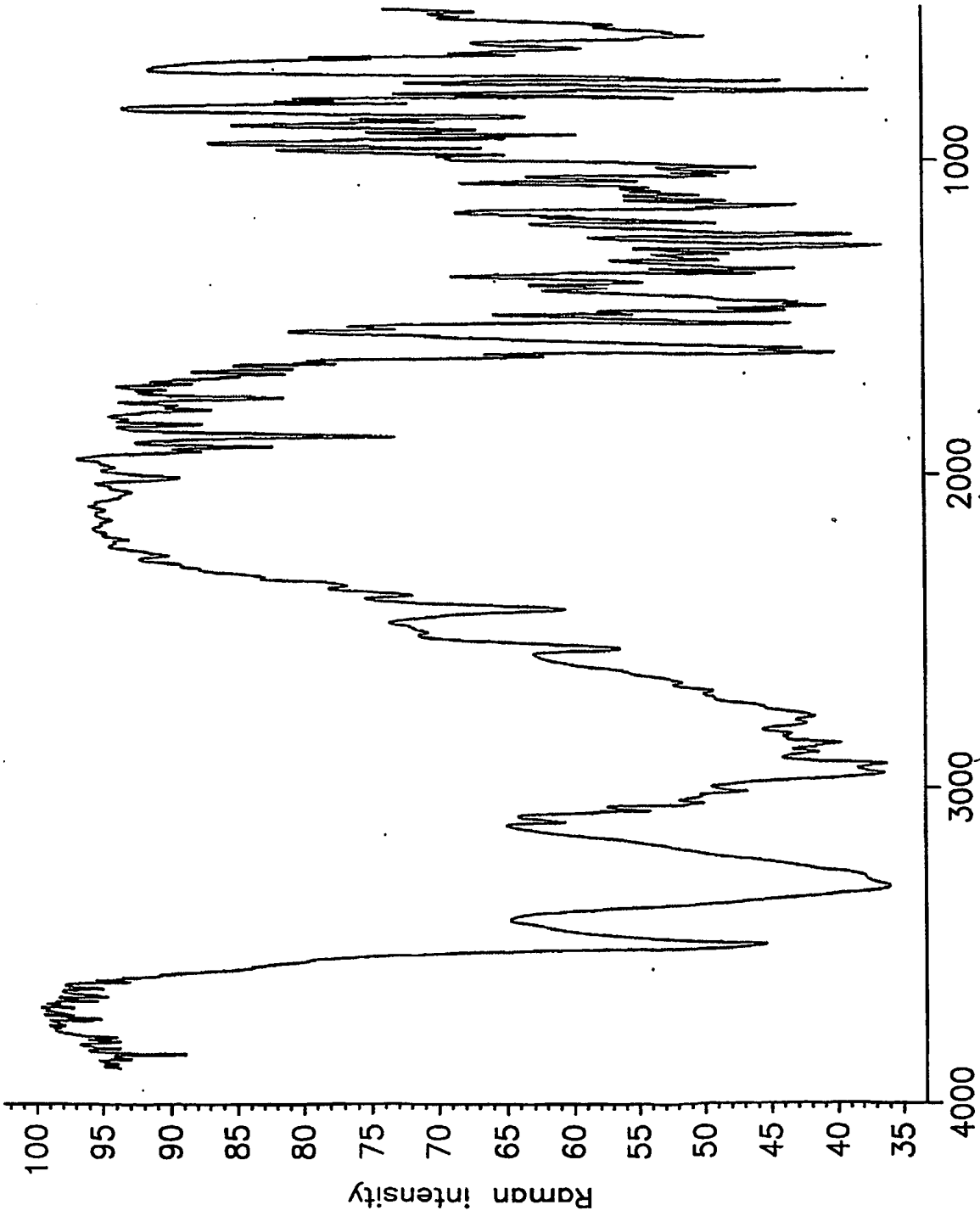

Raman intensity
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 22

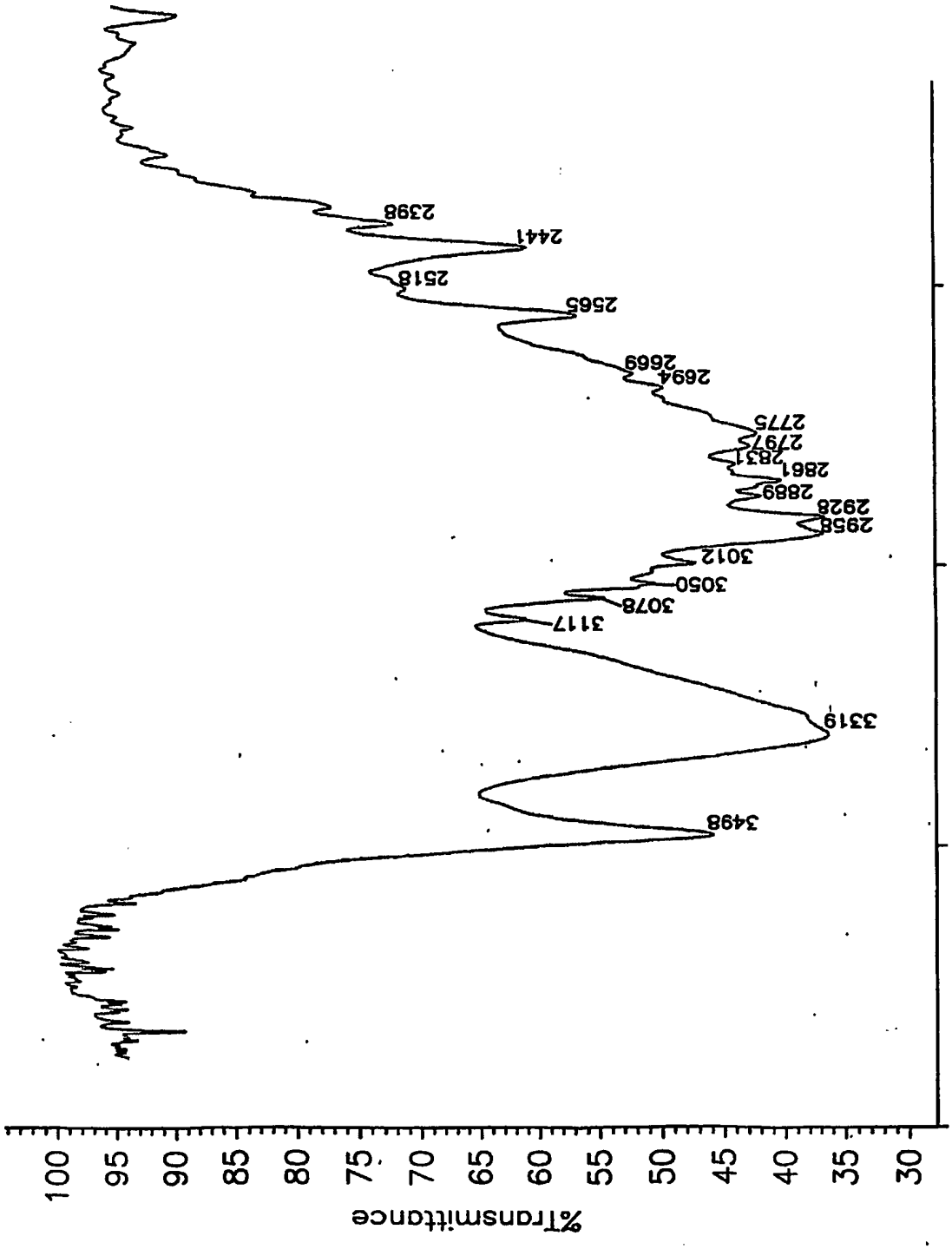

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
Wavenumbers (cm-1)
3498
3319
3117
3078
3050
3012
2958
2928
2889
2861
2831
2797
2775
2694
2669
2565
2518
2441
2398

FIG. 23

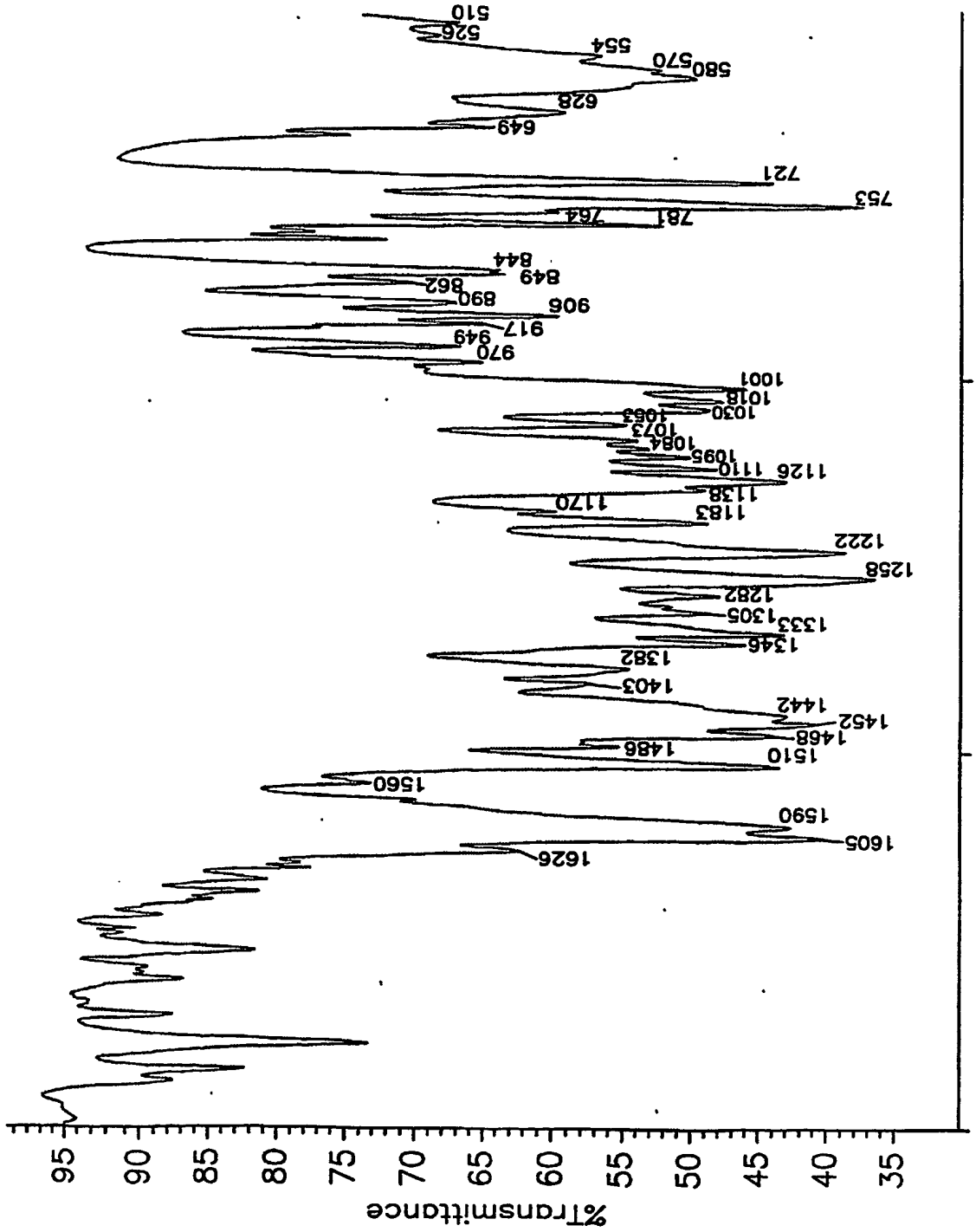

%Transmittance
95
90
85
80
75
70
65
60
55
50
45
40
35
2000
1500
1000
Wavenumbers (cm−1)
510
526
554
580
570
628
649
721
753
781
764
844
849
862
890
906
917
949
970
1001
1018
1030
1063
1073
1084
1095
1110
1126
1138
1170
1183
1222
1258
1282
1305
1333
1346
1382
1403
1442
1452
1468
1486
1510
1560
1590
1605
1626

FIG. 24

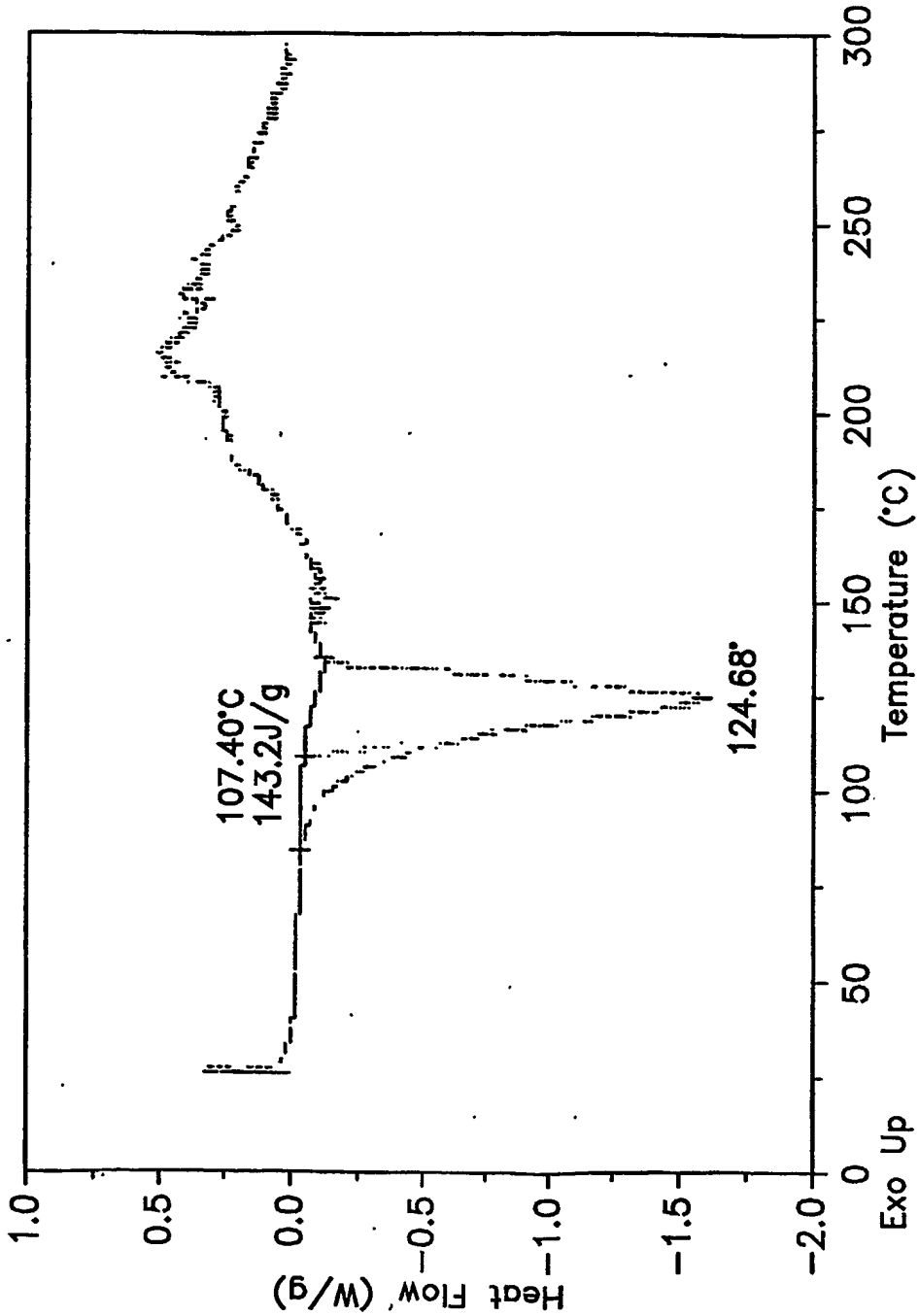

Heat Flow (W/g)
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
Exo Up
0
50
100
150
200
250
300
Temperature (°C)
107.40°C
143.2J/g
124.68°

FIG. 25

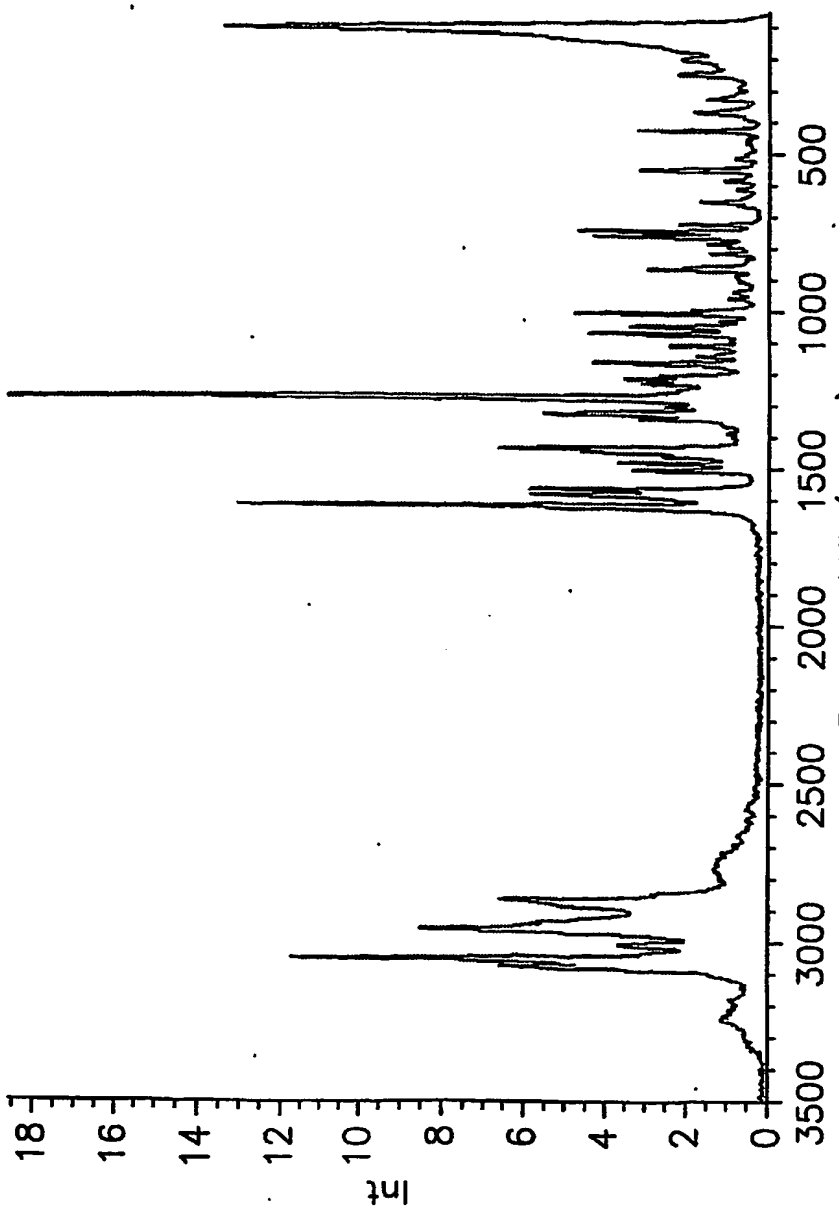

Int
18
16
14
12
10
8
6
4
2
0
3500
3000
2500
2000
1500
1000
500
Raman shift (cm−1)

FIG. 26

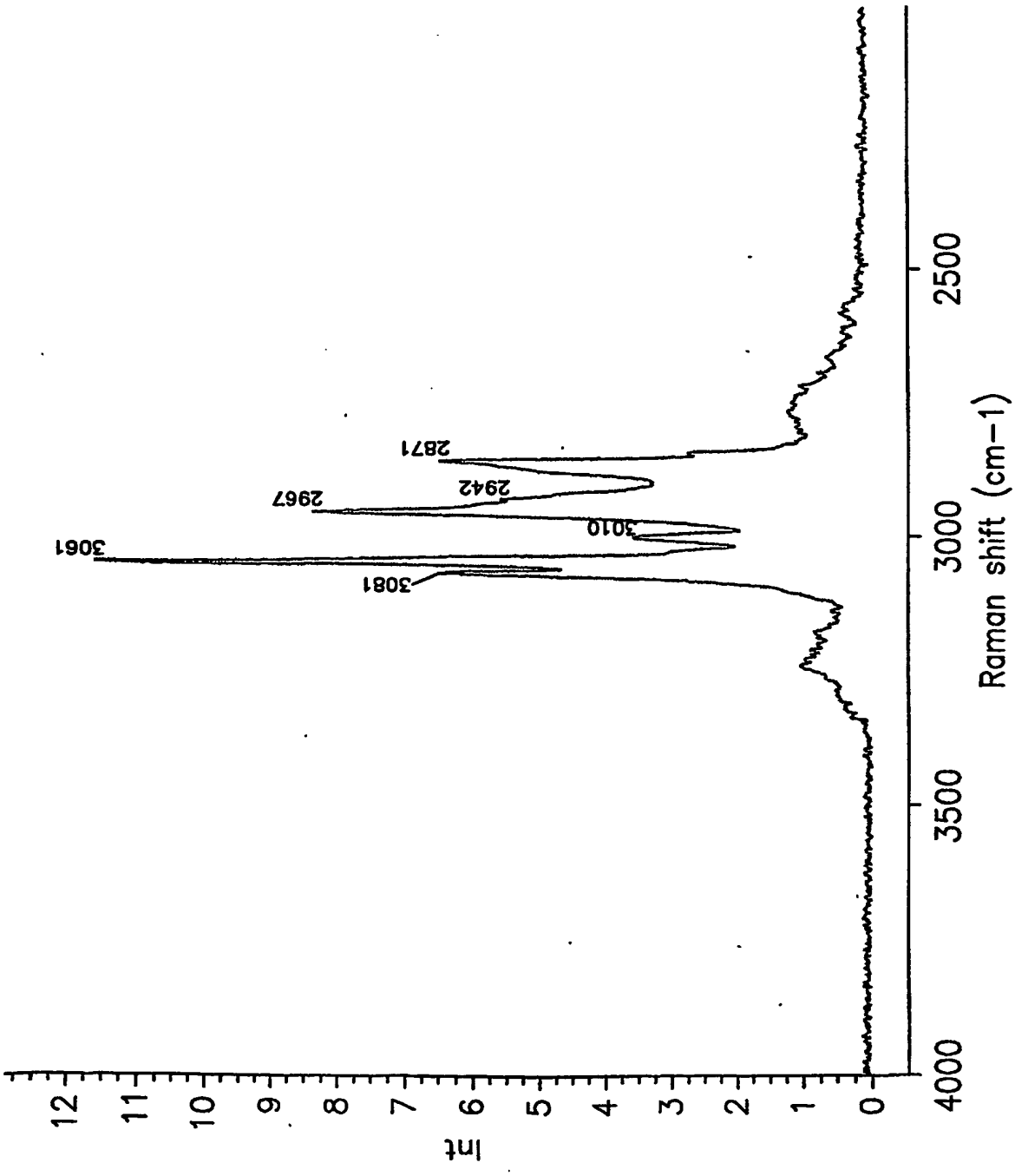

Int
0
1
2
3
4
5
6
7
8
9
10
11
12
4000
3500
3000
2500
Raman shift (cm−1)
3081
3061
3010
2967
2942
2871

FIG. 27

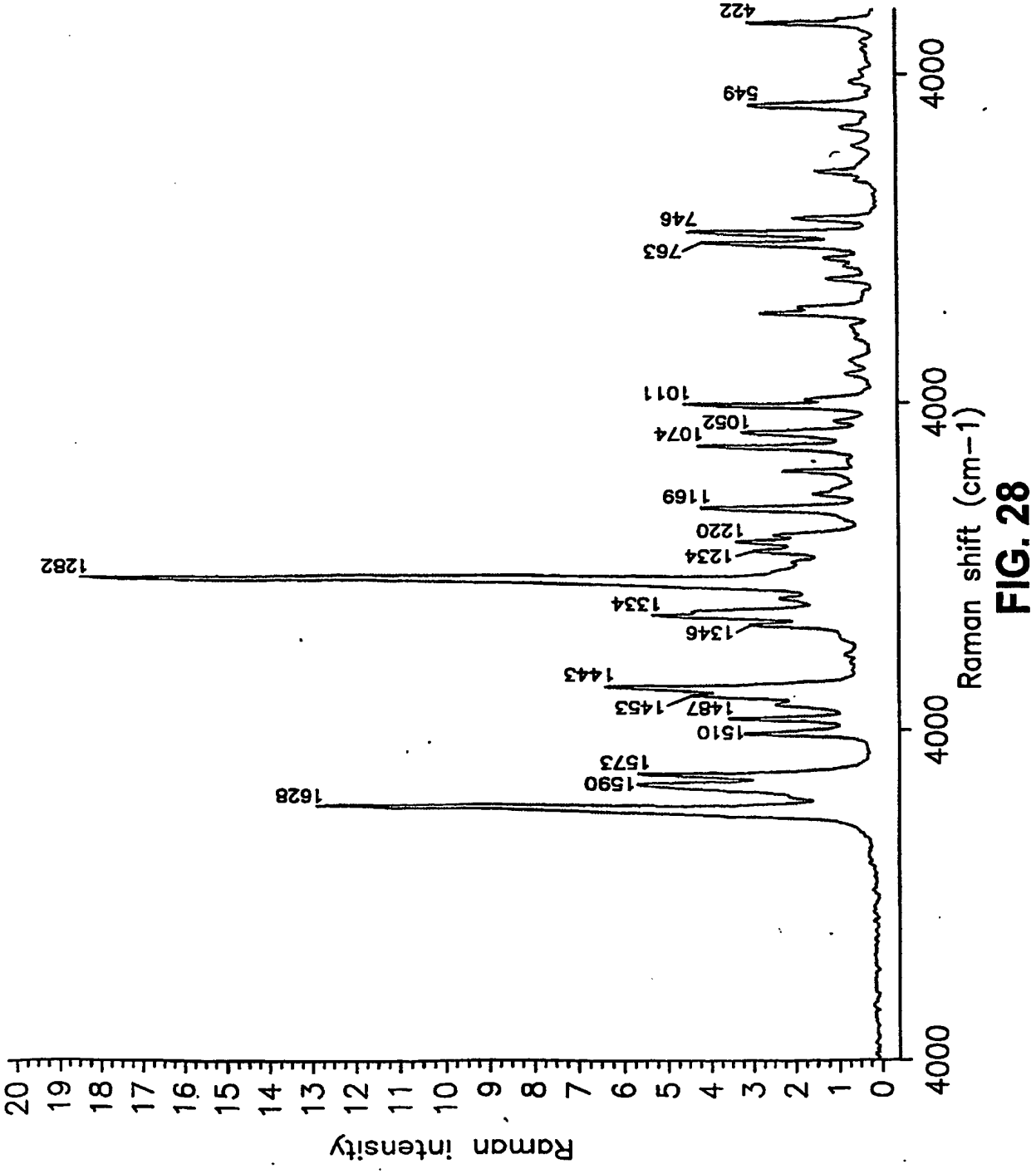

Raman intensity
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
4000
4000
4000
Raman shift (cm−1)
422
549
746
763
1011
1052
1074
1169
1220
1234
1282
1334
1346
1443
1453
1487
1510
1573
1590
1628

FIG. 28

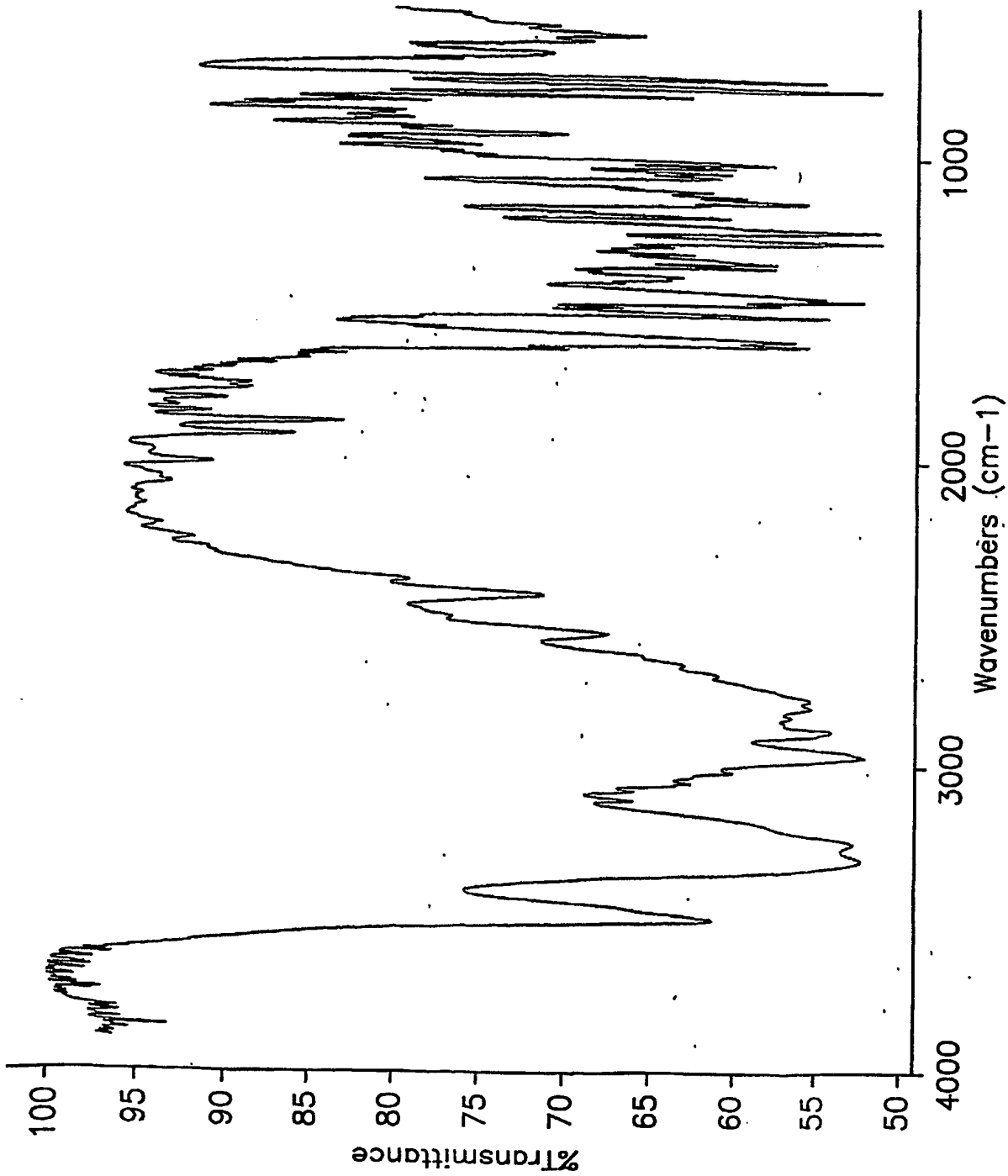

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 29

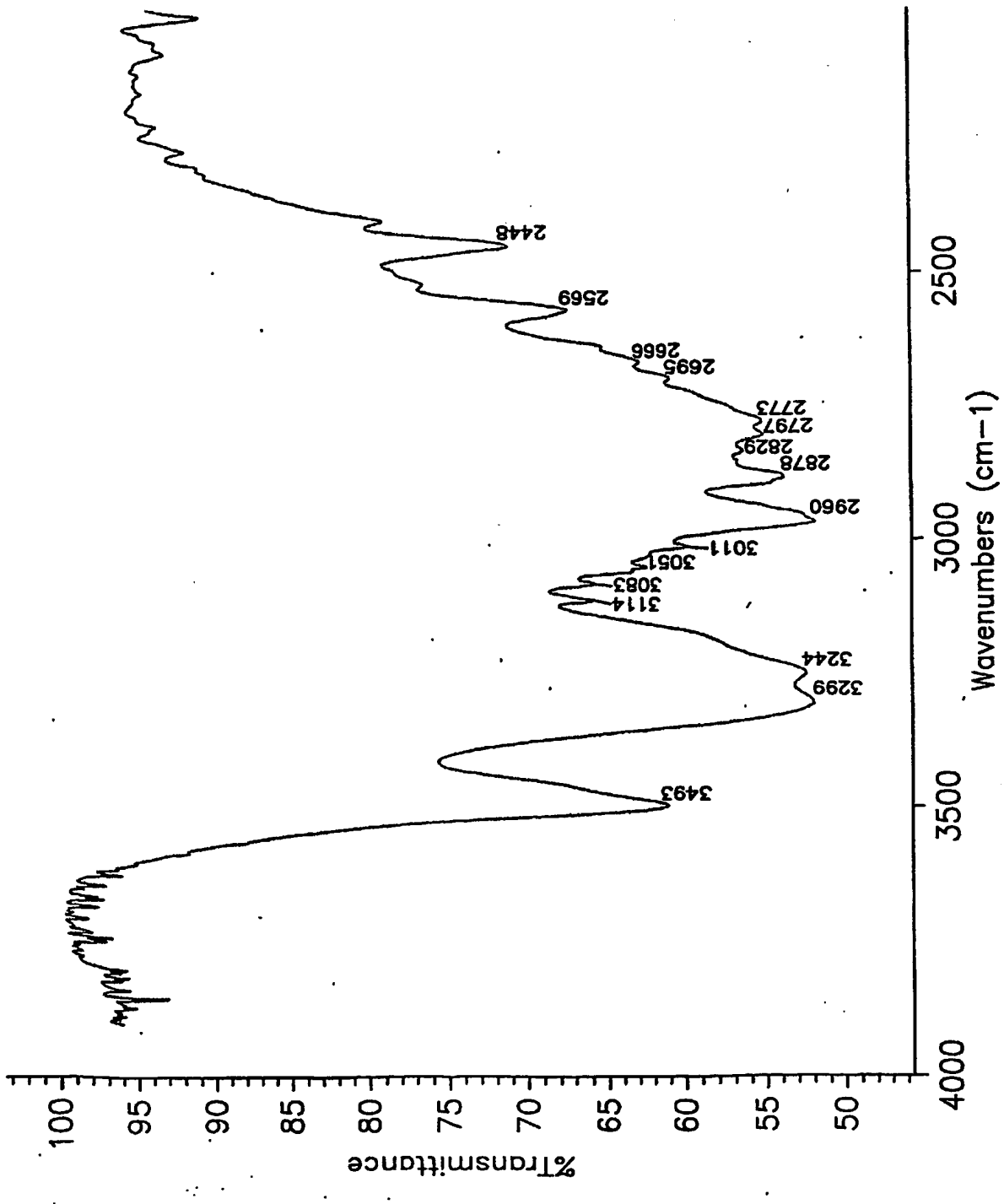

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
4000
3500
3000
2500
Wavenumbers (cm−1)
3493
3299
3244
3114
3083
3051
3011
2960
2878
2829
2797
2773
2695
2666
2569
2448

FIG. 30

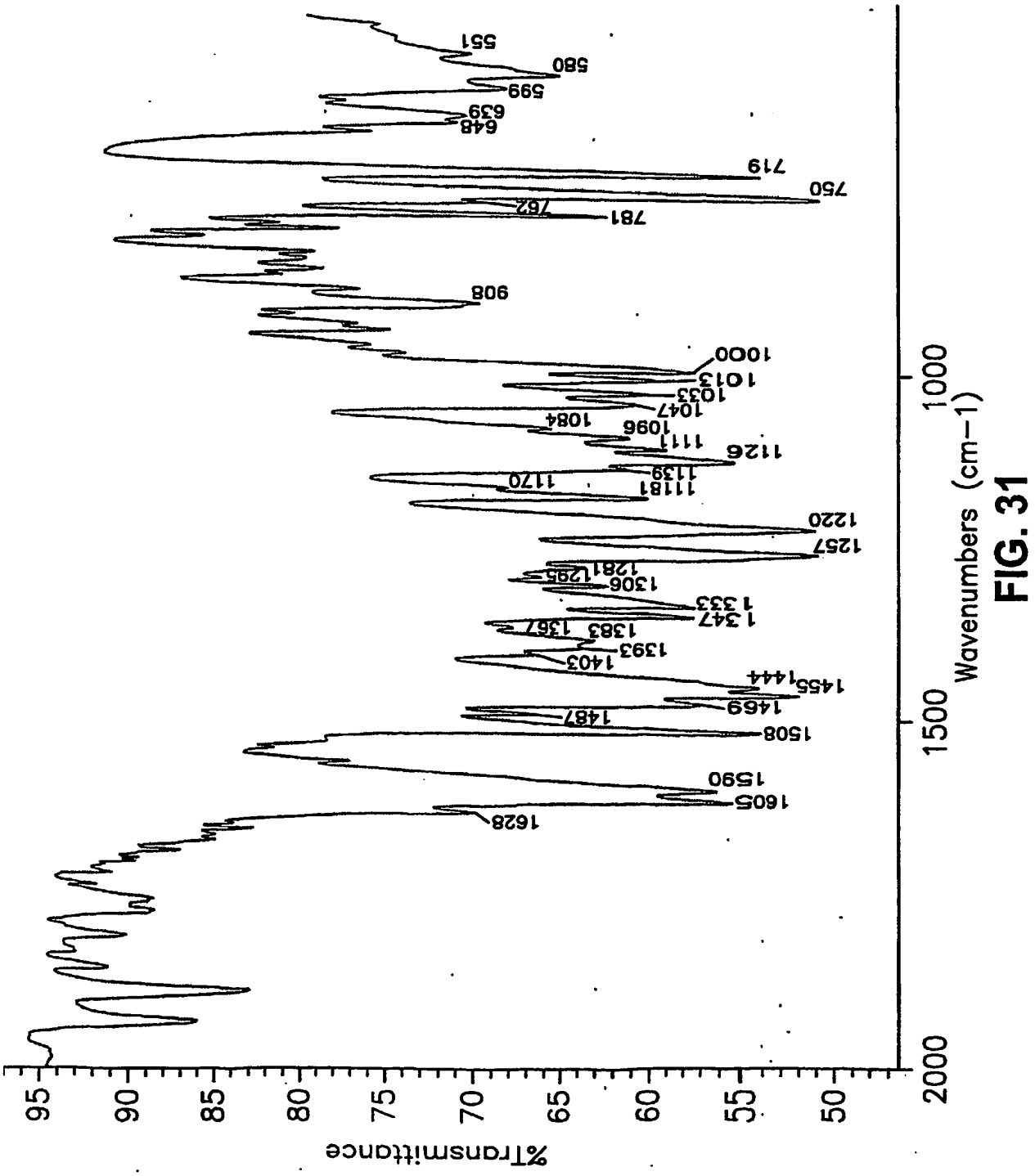

%Transmittance
95
90
85
80
75
70
65
60
55
50
2000
1500
1000
Wavenumbers (cm−1)
551
580
599
639
648
719
750
762
781
908
1000
1013
1033
1047
1084
1096
1111
1126
1139
1170
1181
1220
1257
1281
1295
1306
1333
1347
1367
1383
1393
1403
1444
1455
1469
1487
1508
1590
1605
1628

FIG. 31

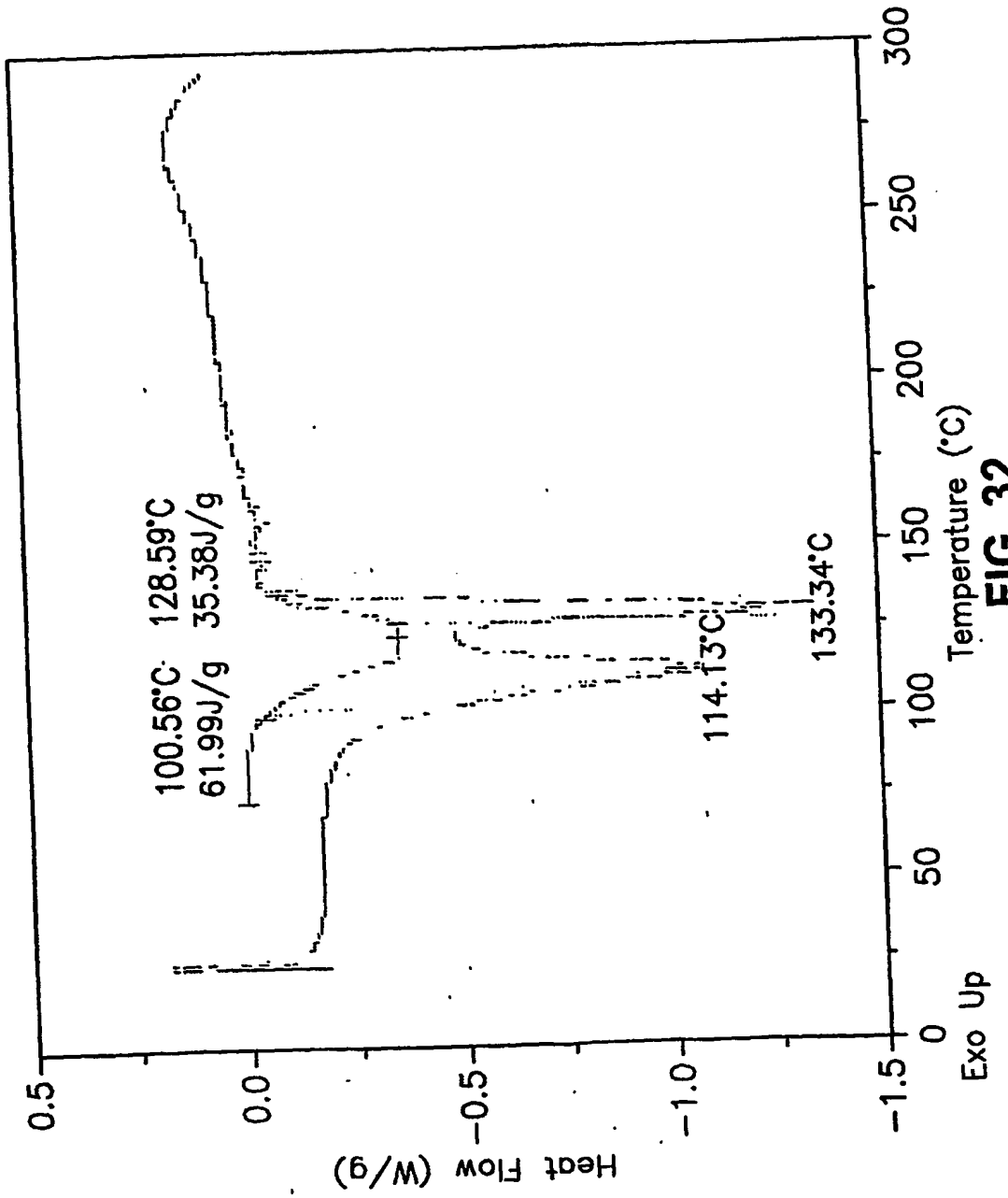

100.56°C
61.99J/g
128.59°C
35.38J/g
114.13°C
133.34°C
Heat Flow (W/g)
0.5
0.0
−0.5
−1.0
−1.5
Exo Up
0
50
100
150
200
250
300
Temperature (°C)

FIG. 32

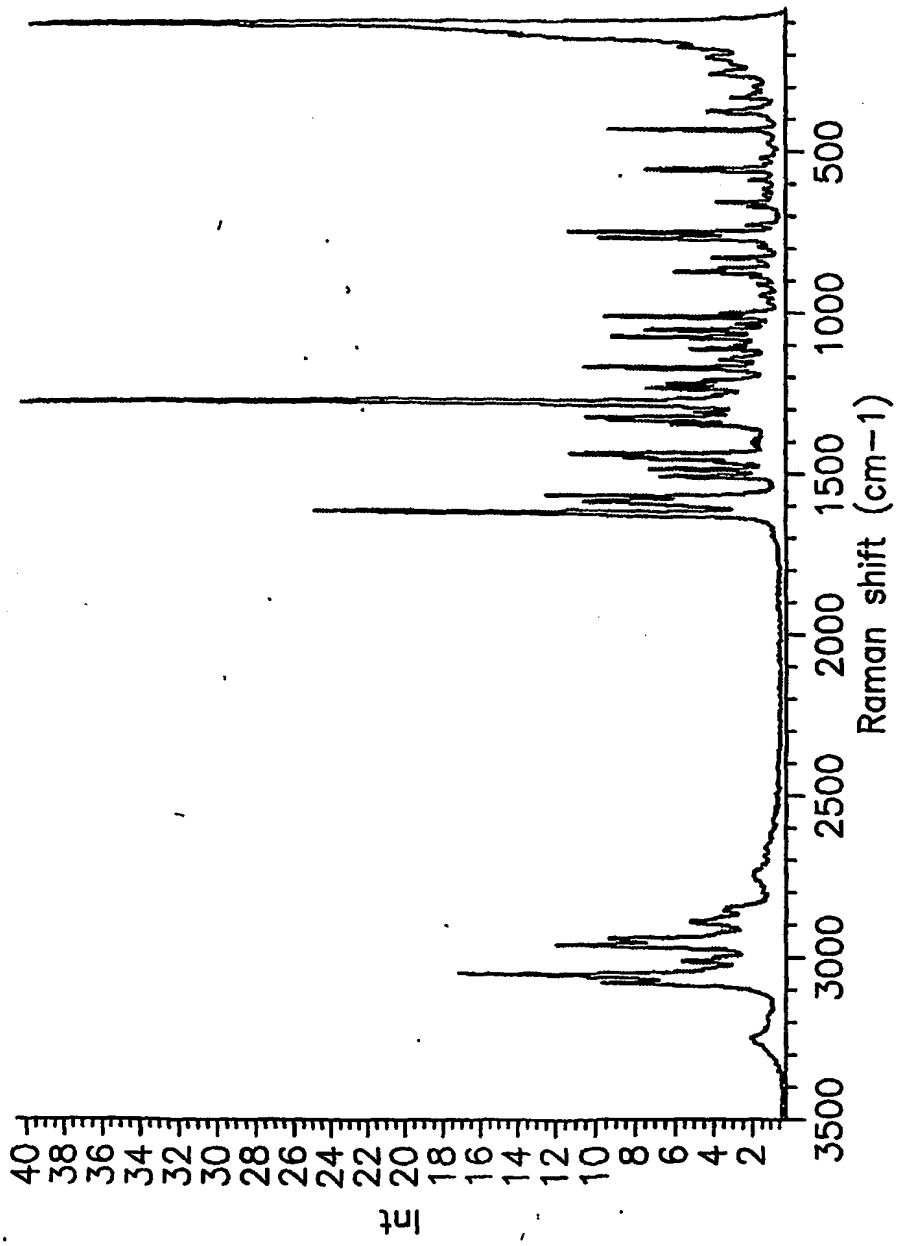

Int
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
3500
3000
2500
2000
1500
1000
500
Raman shift (cm−1)

FIG. 33

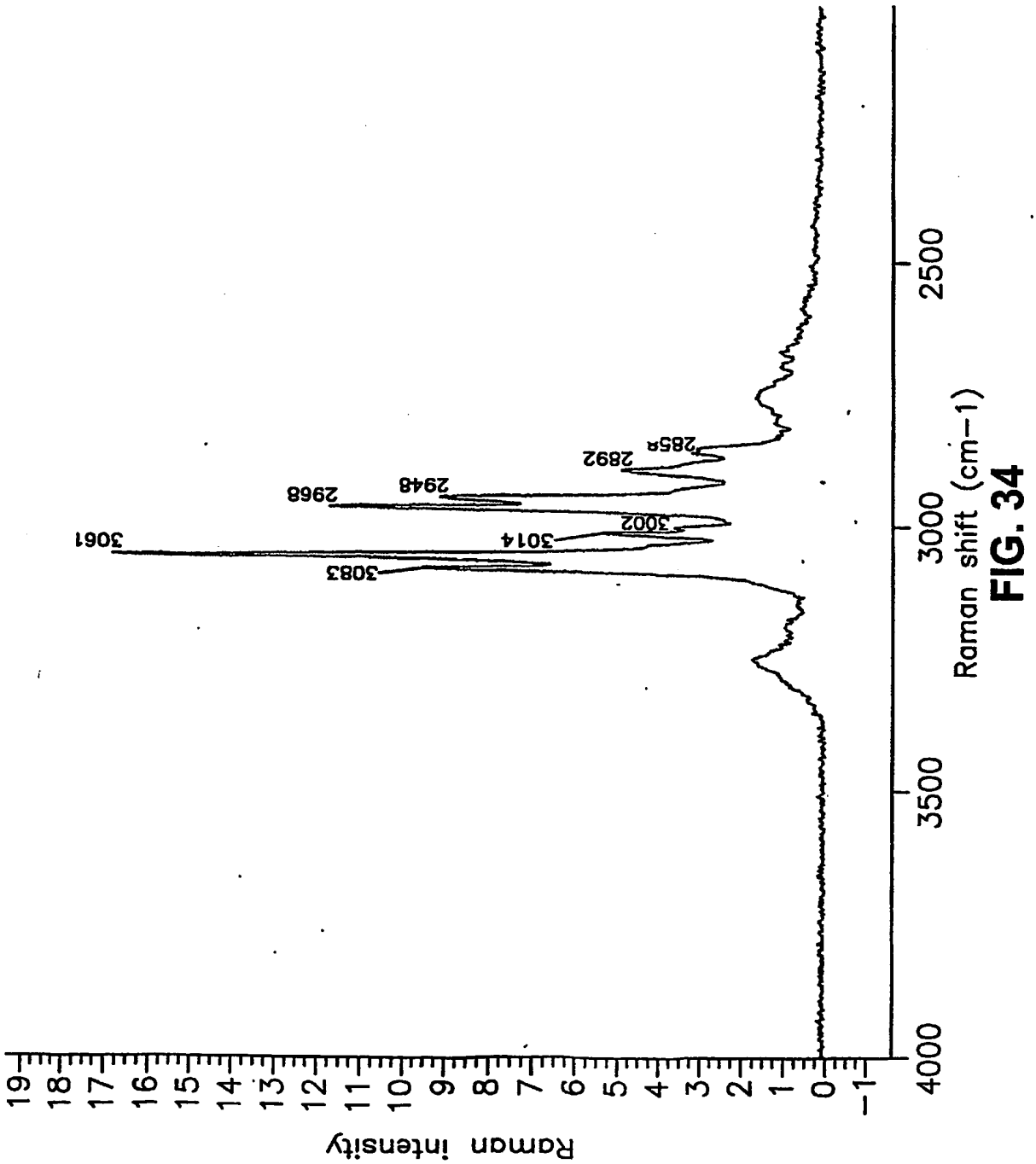

Raman intensity
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
4000
3500
3000
2500
Raman shift (cm−1)
3061
3083
3014
3002
2968
2948
2892
2858

FIG. 34

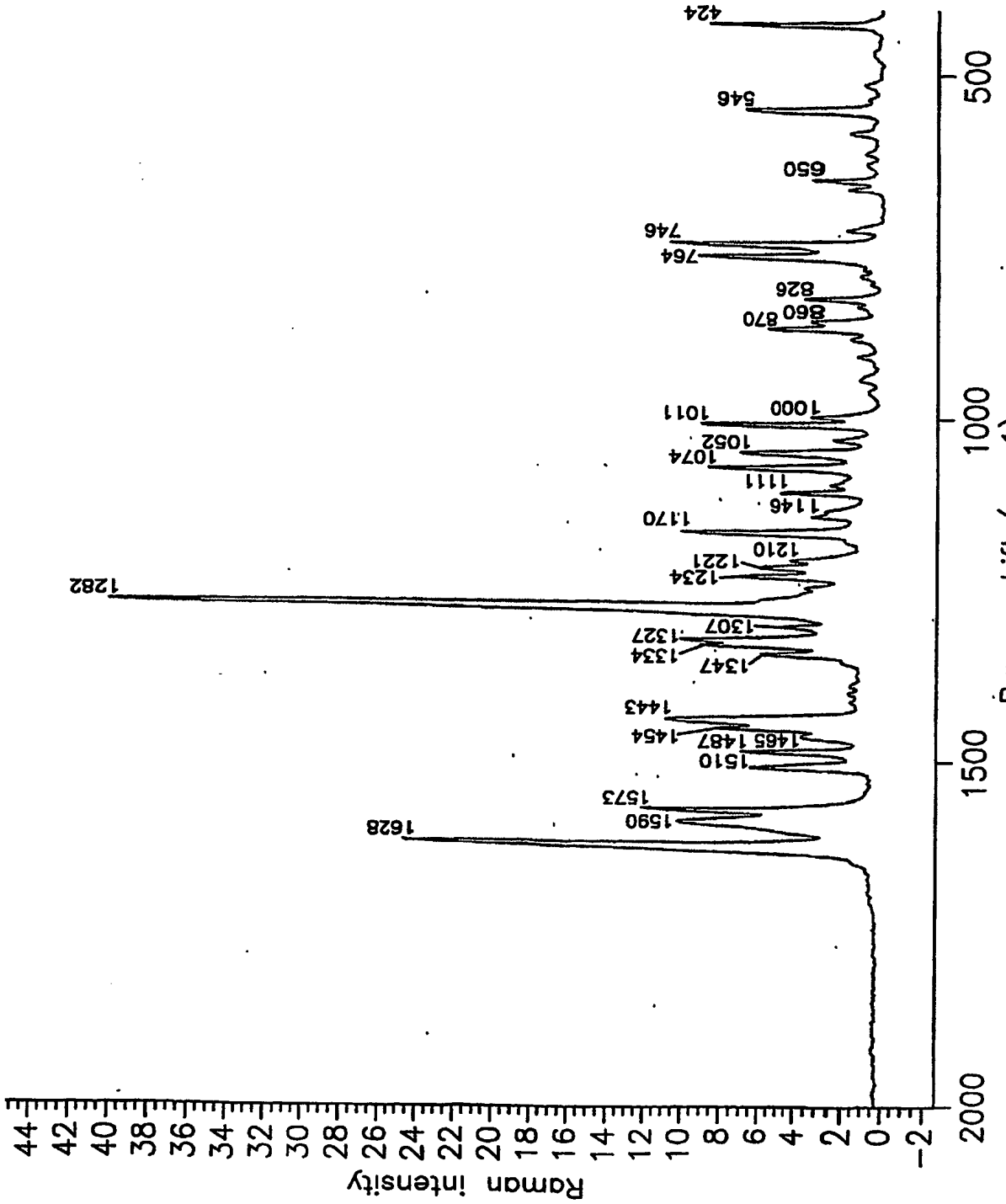

Raman intensity
44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2
2000
1500
1000
500
Raman shift (cm-1)
424
546
650
746
764
826
860
870
1000
1011
1052
1074
1111
1146
1170
1210
1221
1234
1282
1307
1327
1334
1347
1443
1454
1465
1487
1510
1573
1590
1628

FIG. 35

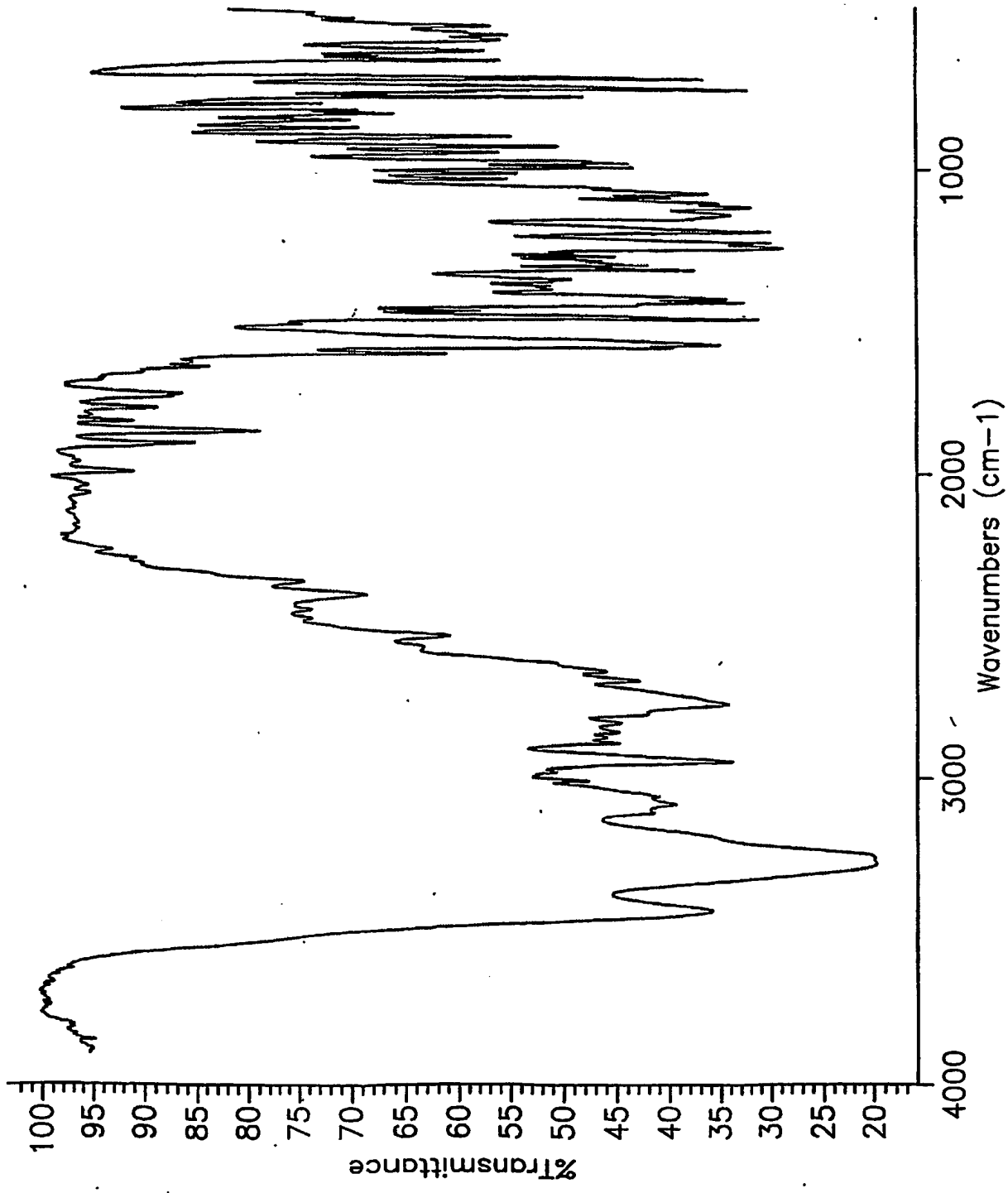

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 36

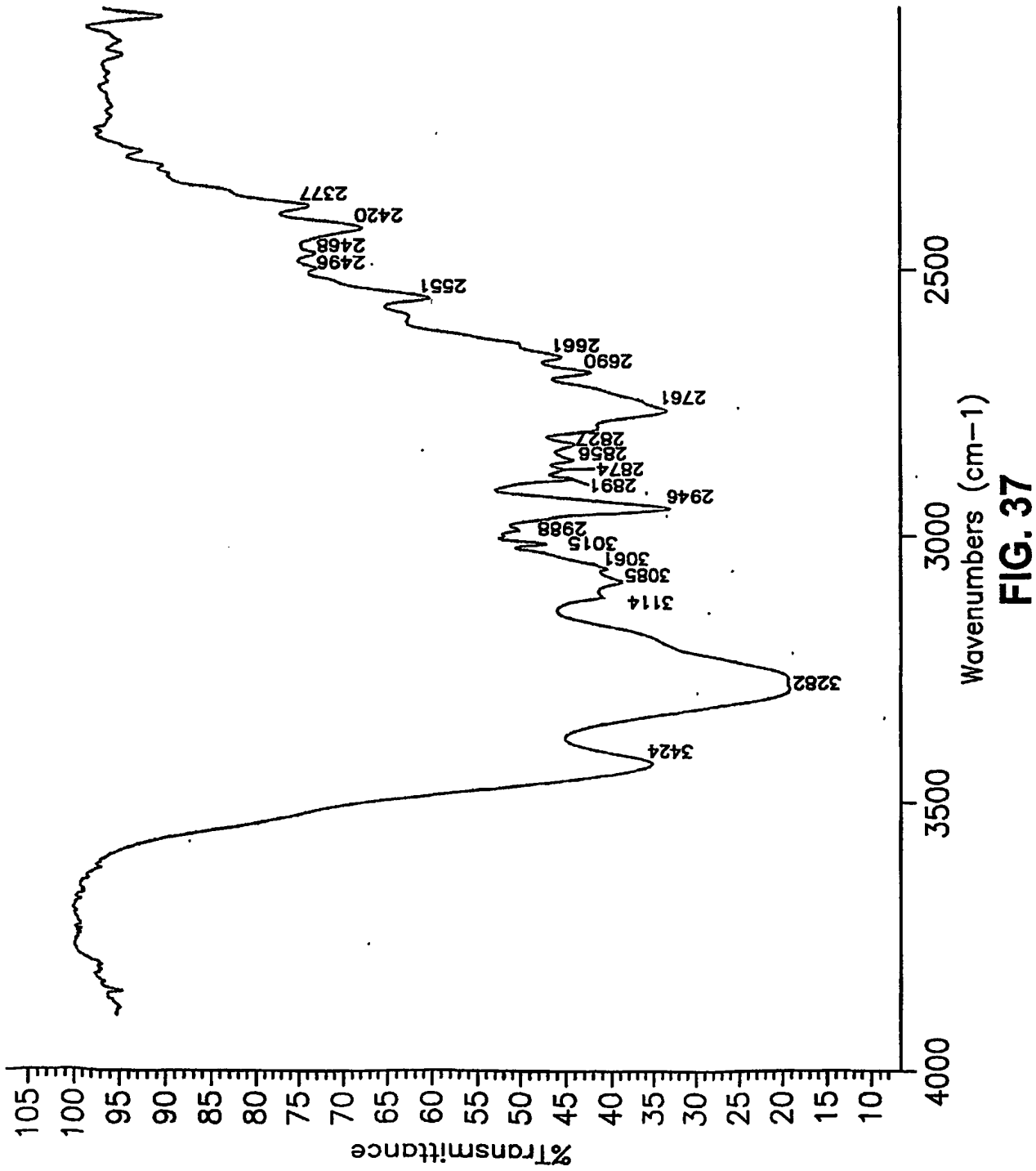

%Transmittance
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
4000
3500
3000
2500
Wavenumbers (cm−1)
3424
3282
3114
3085
3061
3015
2988
2946
2891
2874
2856
2827
2761
2690
2661
2551
2496
2468
2420
2377

FIG. 37

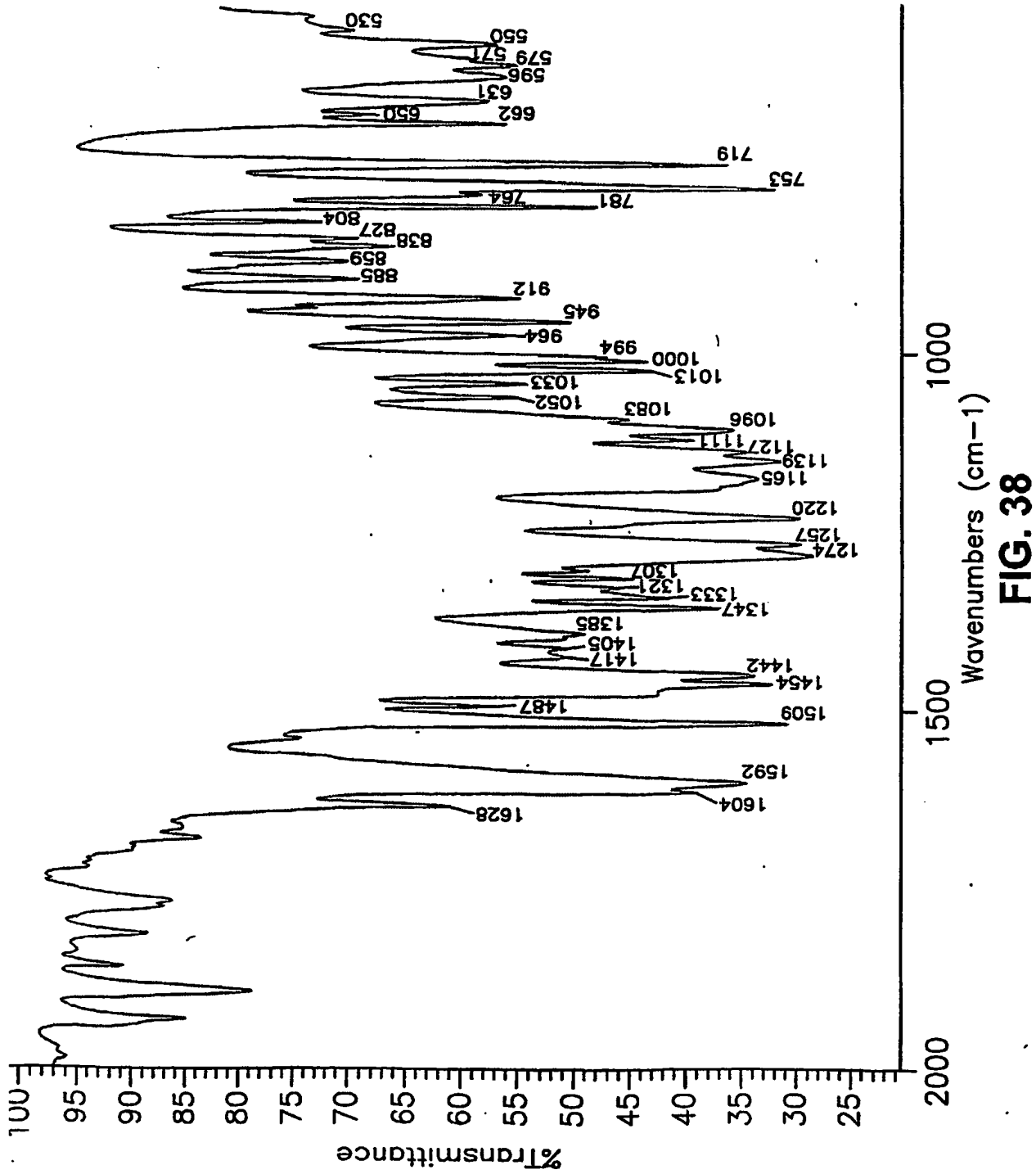

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
2000
1500
1000
Wavenumbers (cm−1)
530
550
571
579
596
631
662
650
719
753
781
764
838
827
804
859
885
912
945
964
994
1000
1013
1033
1052
1083
1096
1127
1111
1139
1165
1220
1257
1274
1307
1321
1333
1347
1385
1405
1417
1442
1454
1487
1509
1592
1604
1628

FIG. 38

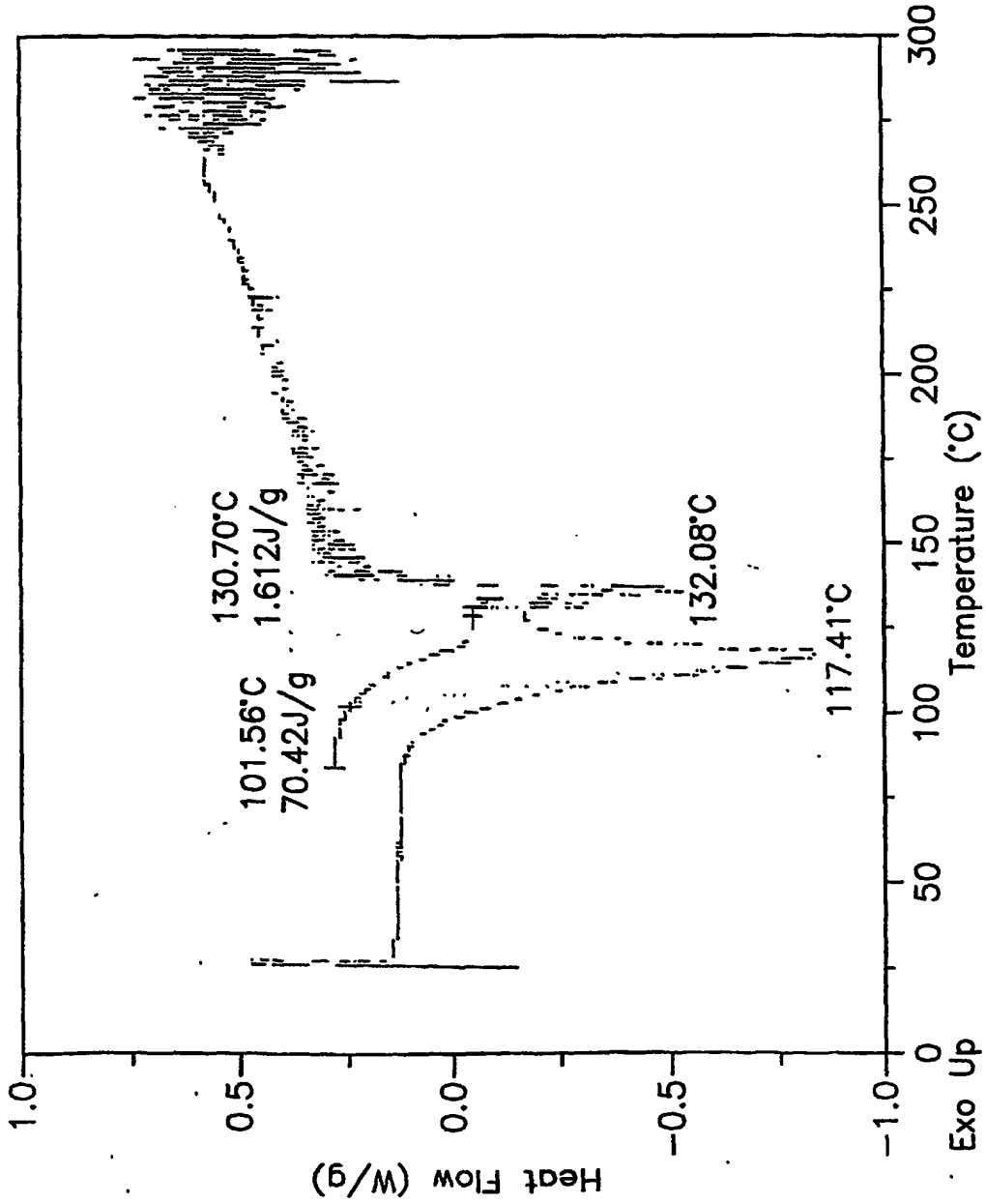

130.70°C
1.612J/g
101.56°C
70.42J/g
132.08°C
117.41°C
Heat Flow (W/g)
1.0
0.5
0.0
-0.5
-1.0
Exo Up
0
50
100
150
200
250
300
Temperature (°C)

FIG. 39

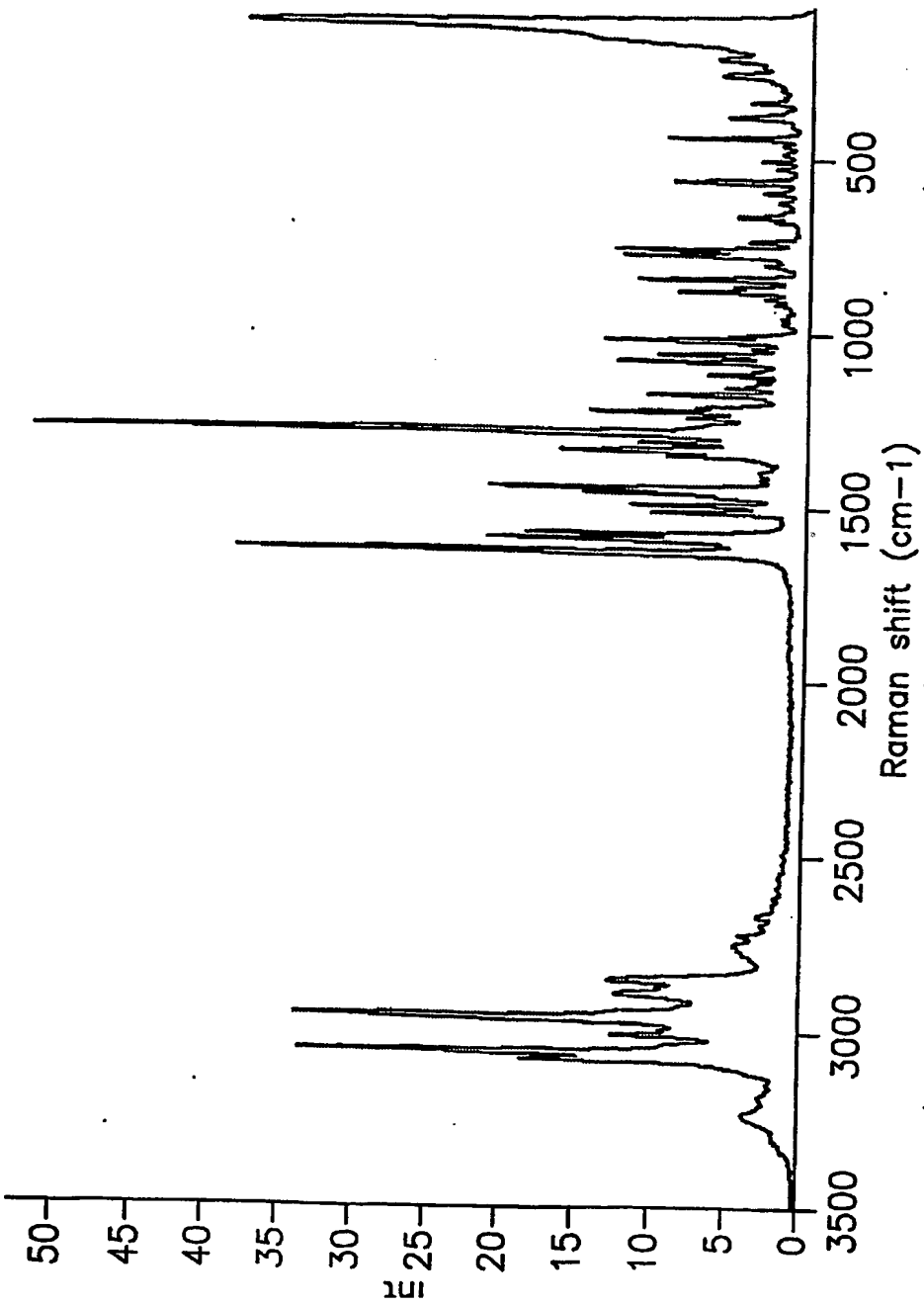

50
45
40
35
30
25
20
15
10
5
0
3500
3000
2500
2000
1500
1000
500
Raman shift (cm−1)

FIG. 40

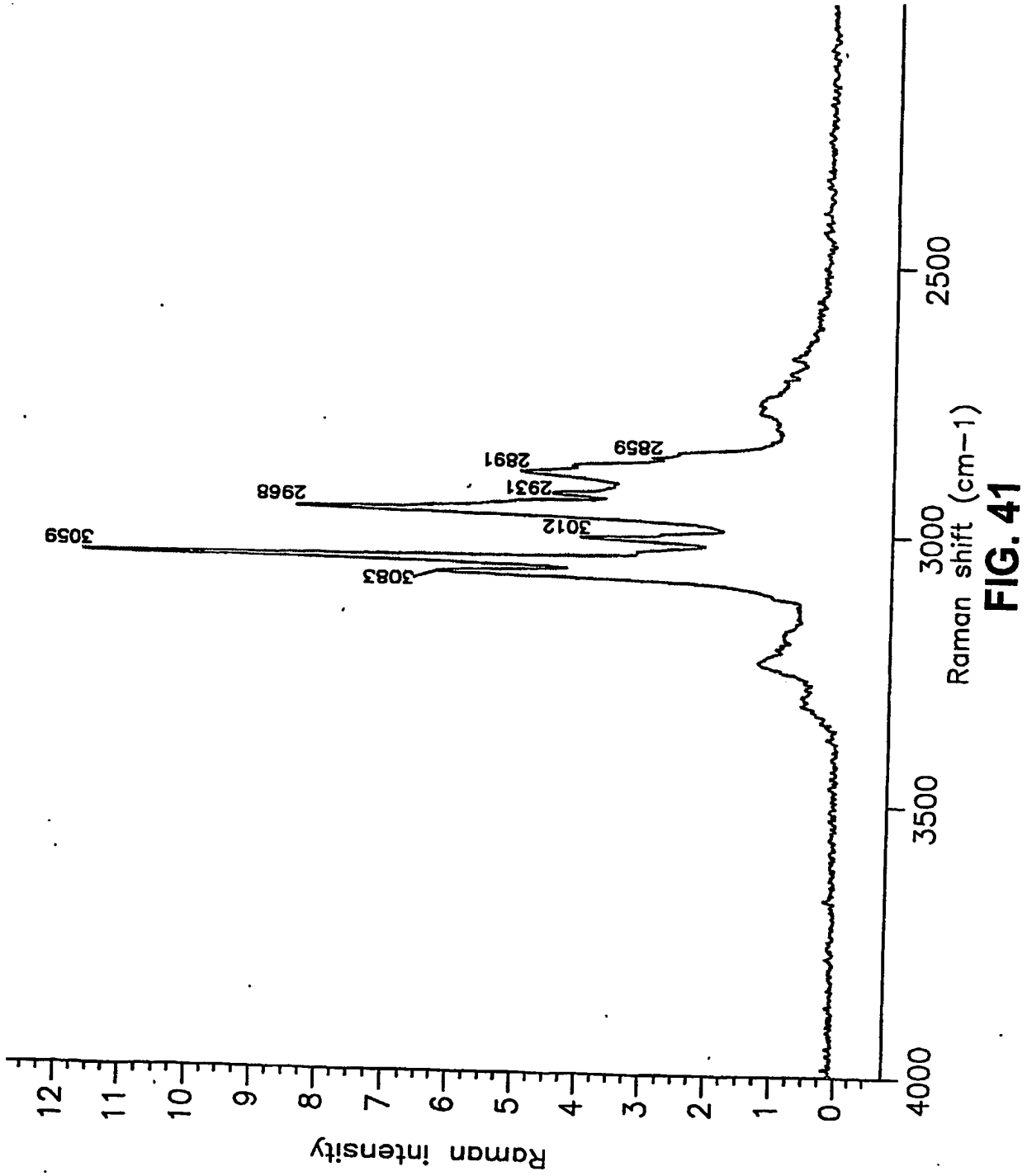

Raman intensity
0
1
2
3
4
5
6
7
8
9
10
11
12
4000
3500
3000
2500
Raman shift (cm−1)
3059
3083
3012
2968
2931
2891
2859

FIG. 41

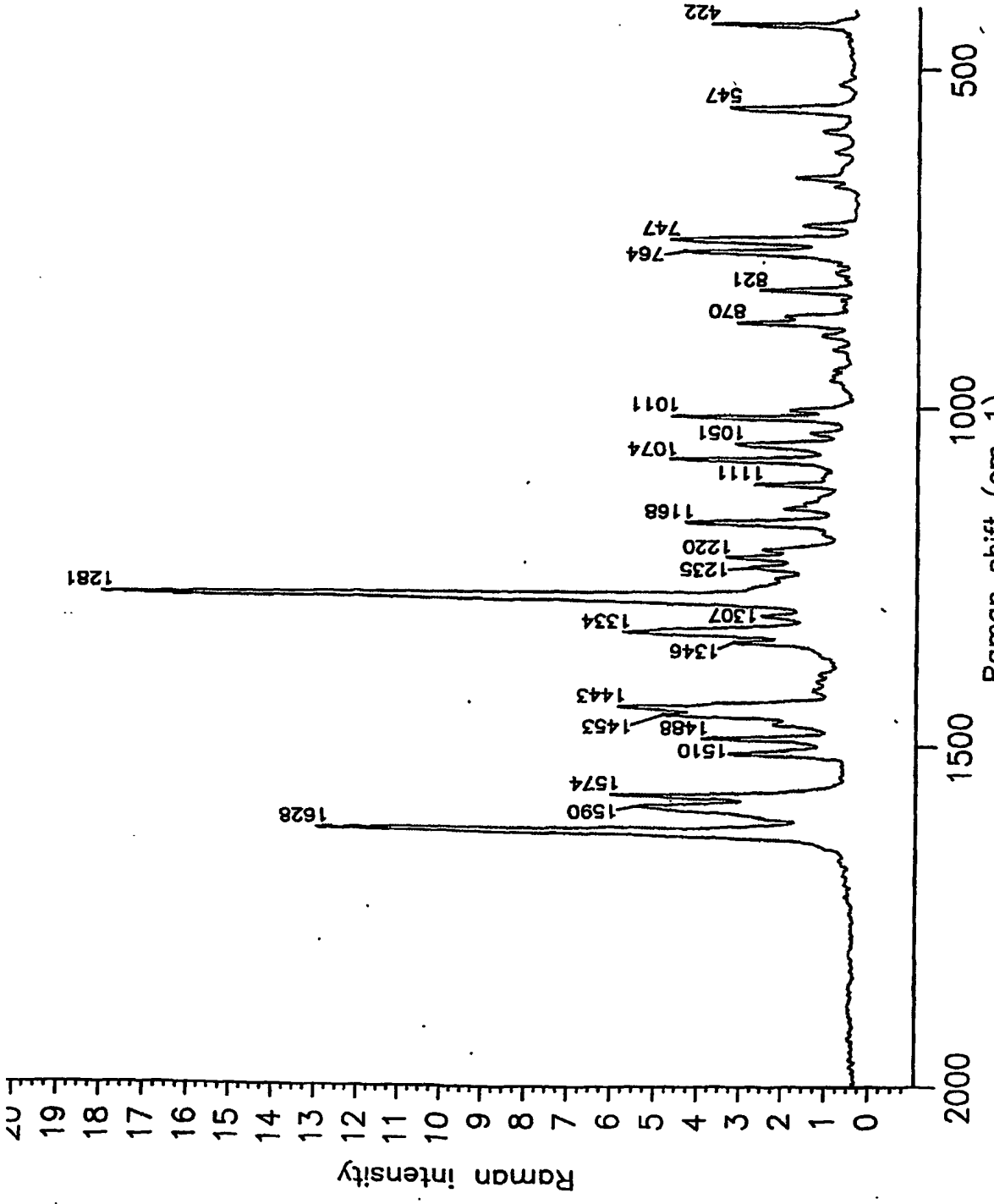

Raman intensity
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Raman shift (cm−1)
500
1000
1500
2000
422
547
747
764
821
870
1011
1051
1074
1111
1168
1220
1235
1281
1307
1334
1346
1443
1453
1488
1510
1574
1590
1628

FIG. 42

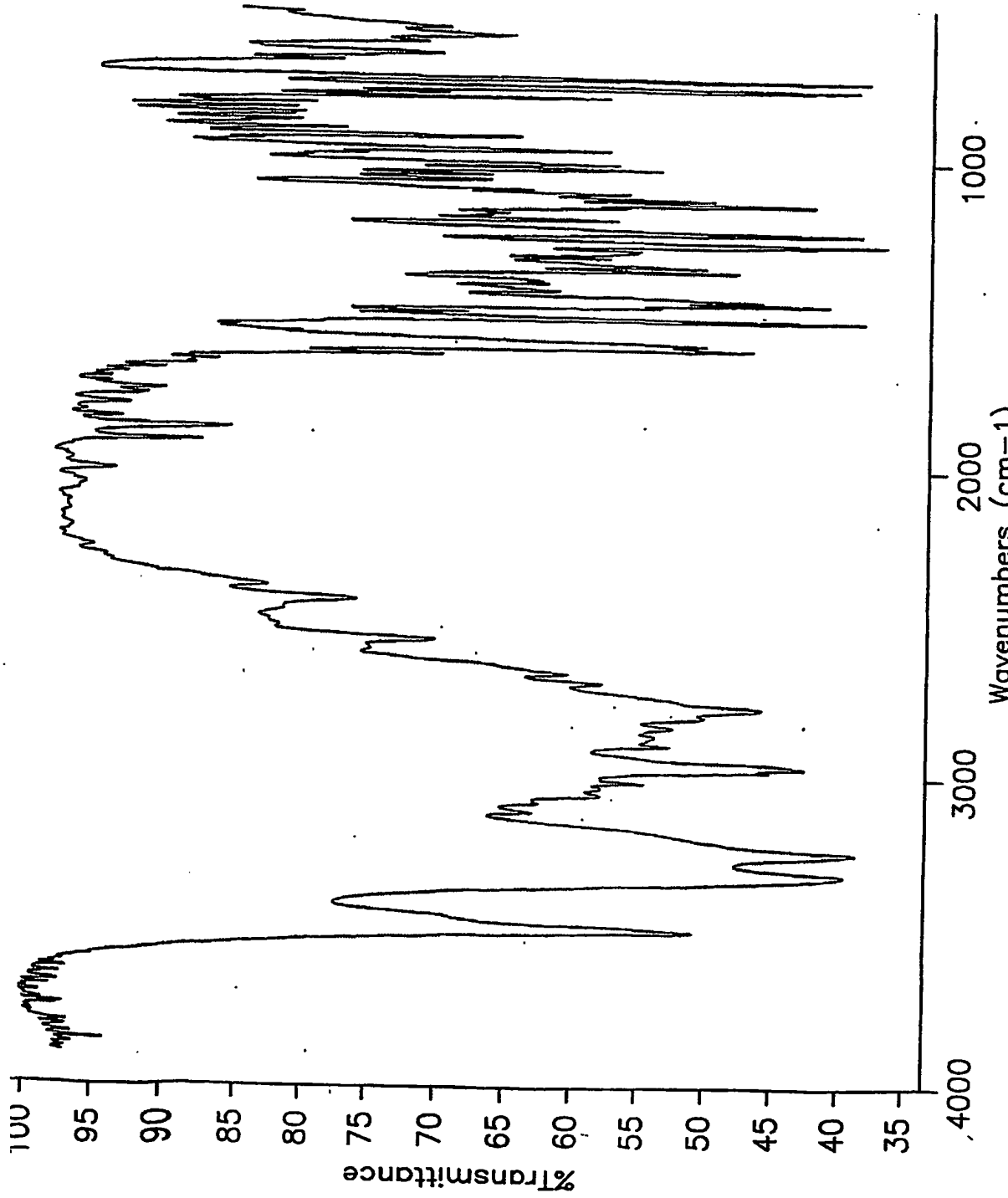

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 43

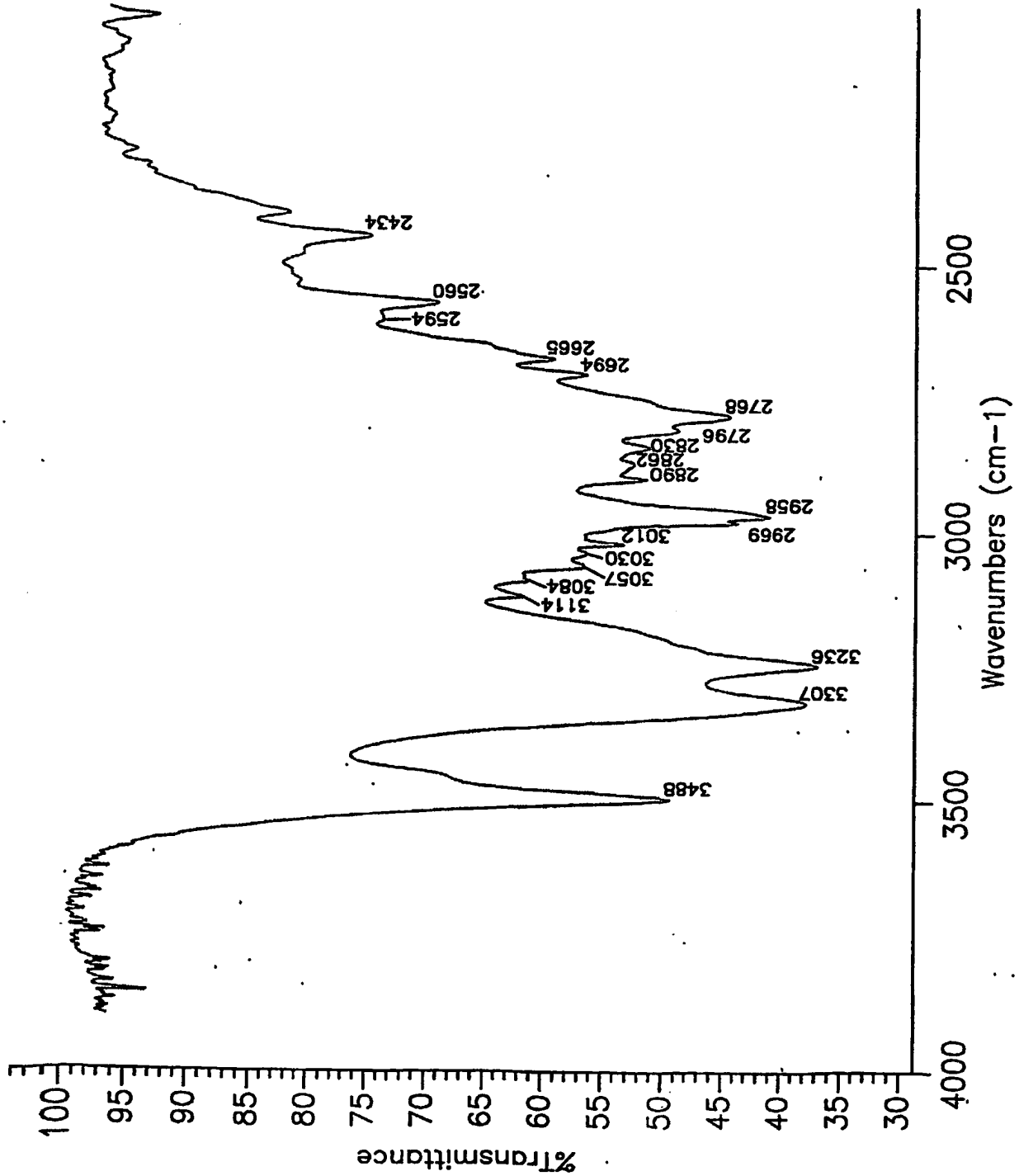

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
4000
3500
3000
2500
Wavenumbers (cm−1)
3488
3307
3236
3114
3084
3057
3030
3012
2969
2958
2890
2862
2830
2796
2768
2694
2665
2594
2560
2434

FIG. 44

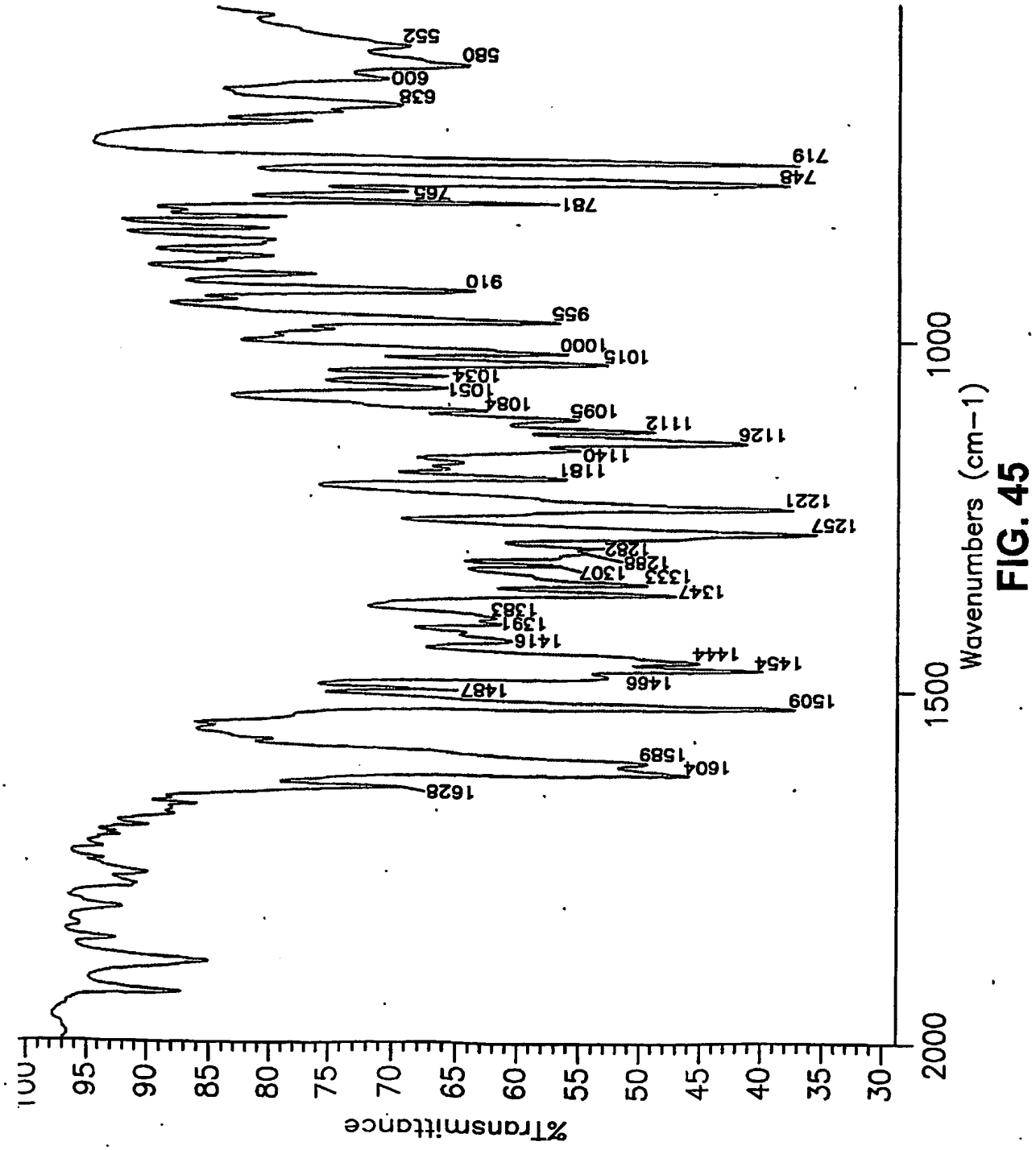

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
2000
1500
1000
Wavenumbers (cm−1)
552
580
600
638
719
748
765
781
910
955
1000
1015
1034
1051
1084
1095
1112
1126
1140
1181
1221
1257
1282
1288
1307
1333
1347
1383
1391
1416
1444
1454
1466
1487
1509
1589
1604
1628

FIG. 45

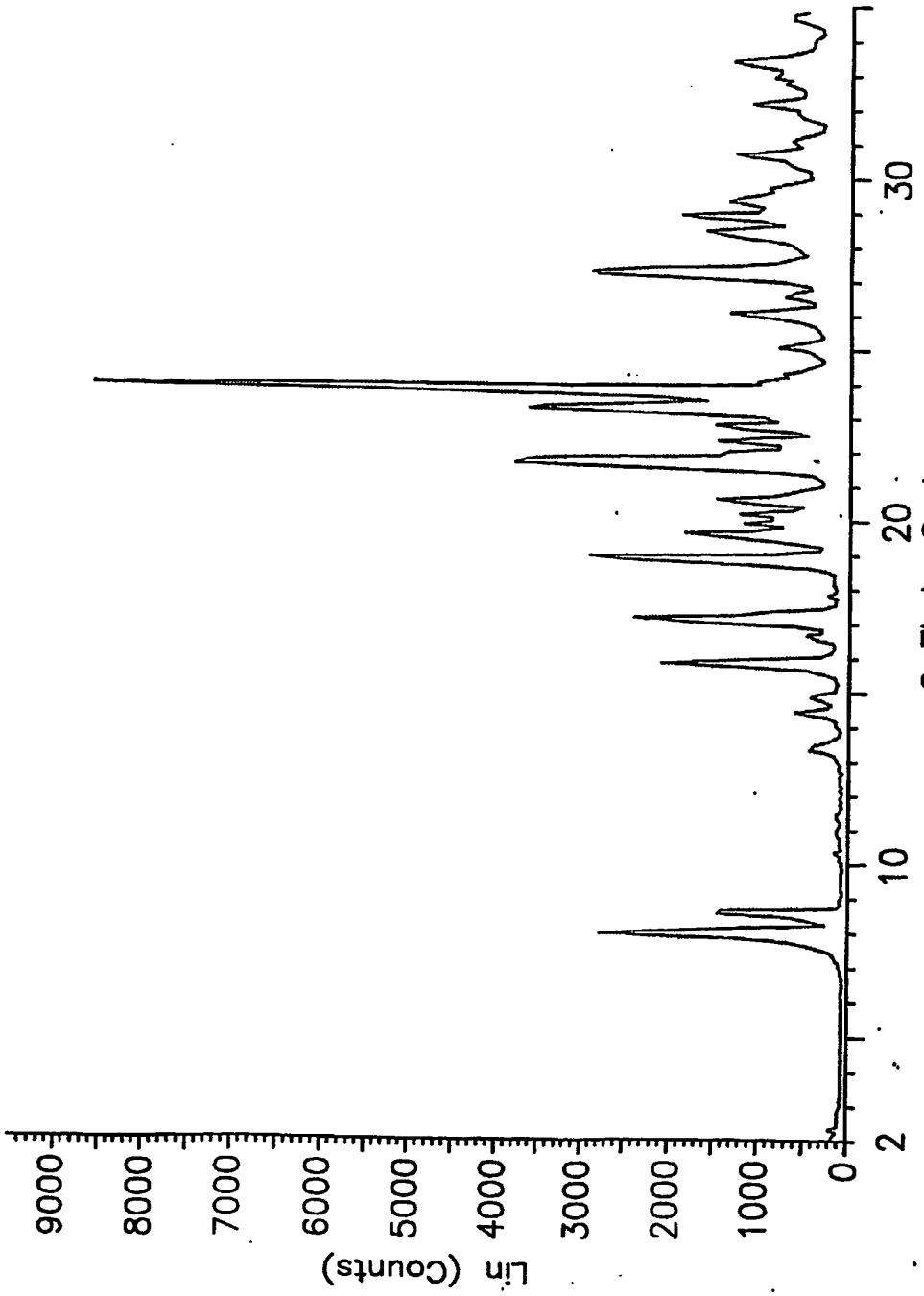

Lin (Counts)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
2-Theta-Scale

FIG. 46

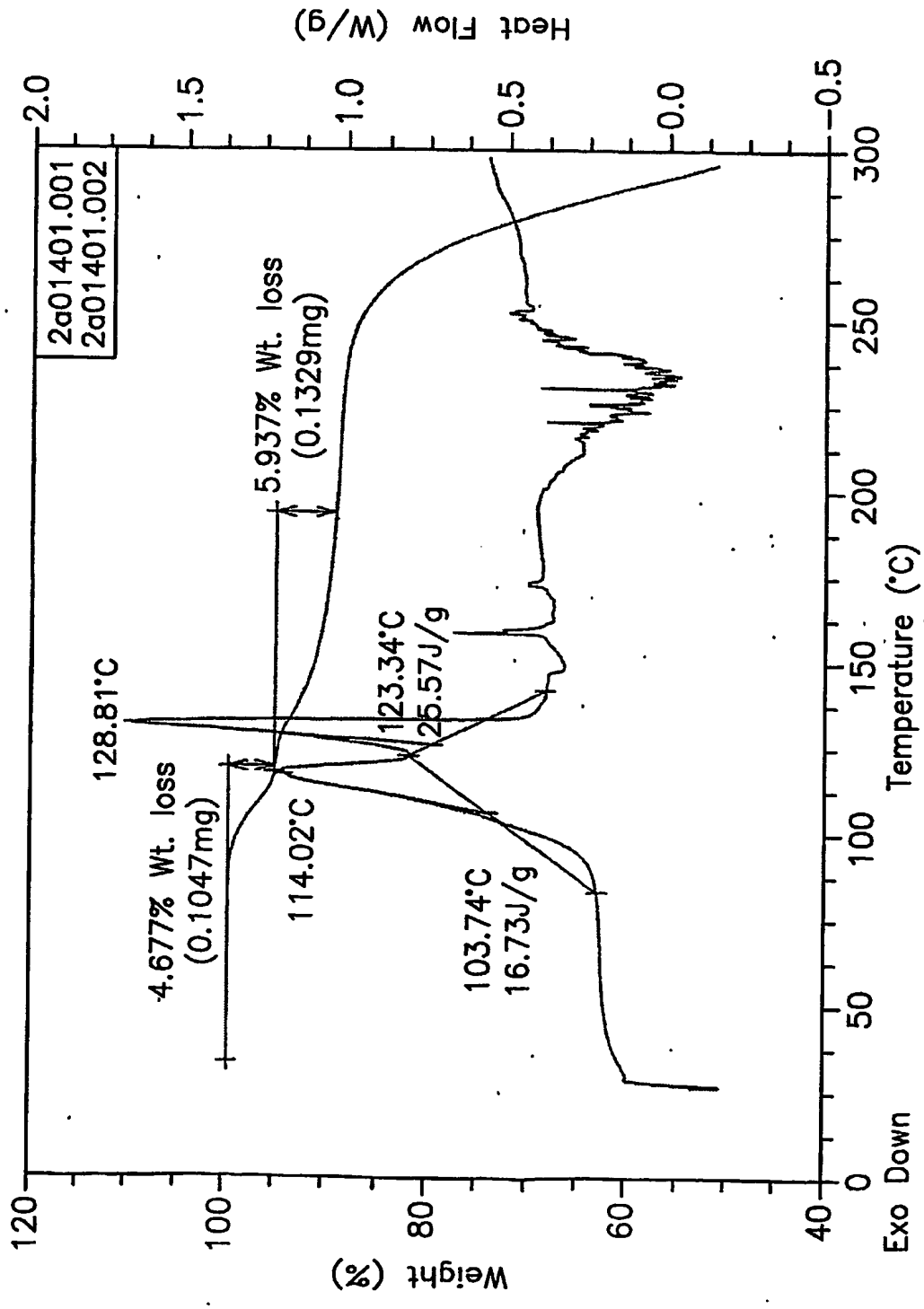

Heat Flow (W/g)
2.0
1.5
1.0
0.5
0.0
-0.5
2a01401.001
2a01401.002
5.937% Wt. loss
(0.1329mg)
128.81°C
123.34°C
25.57J/g
4.677% Wt. loss
(0.1047mg)
114.02°C
103.74°C
16.73J/g
Weight (%)
120
100
80
60
40
0
50
100
150
200
250
300
Temperature (°C)
Exo Down

FIG. 47

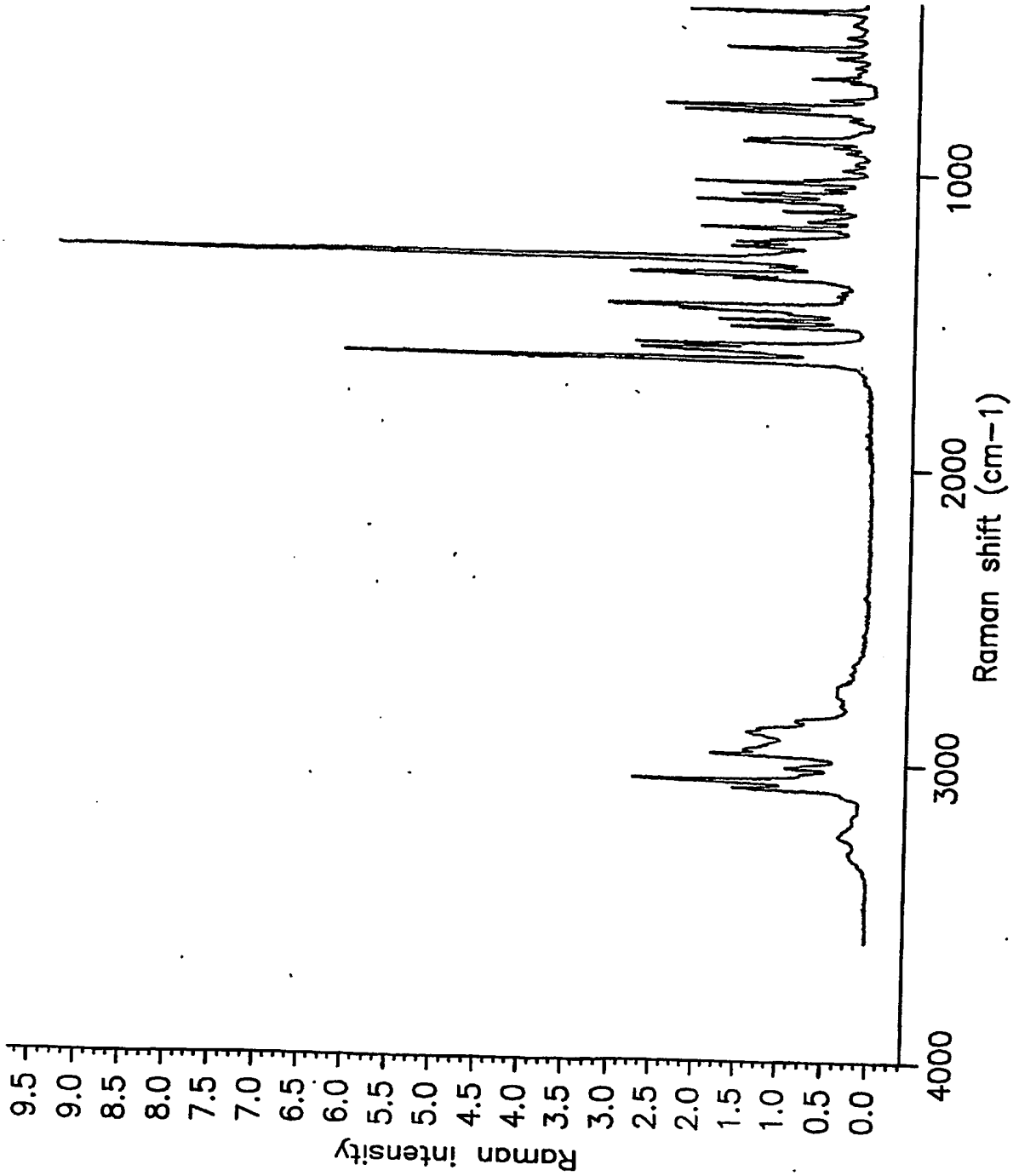

Raman intensity
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4000
3000
2000
1000
Raman shift (cm−1)

FIG. 48

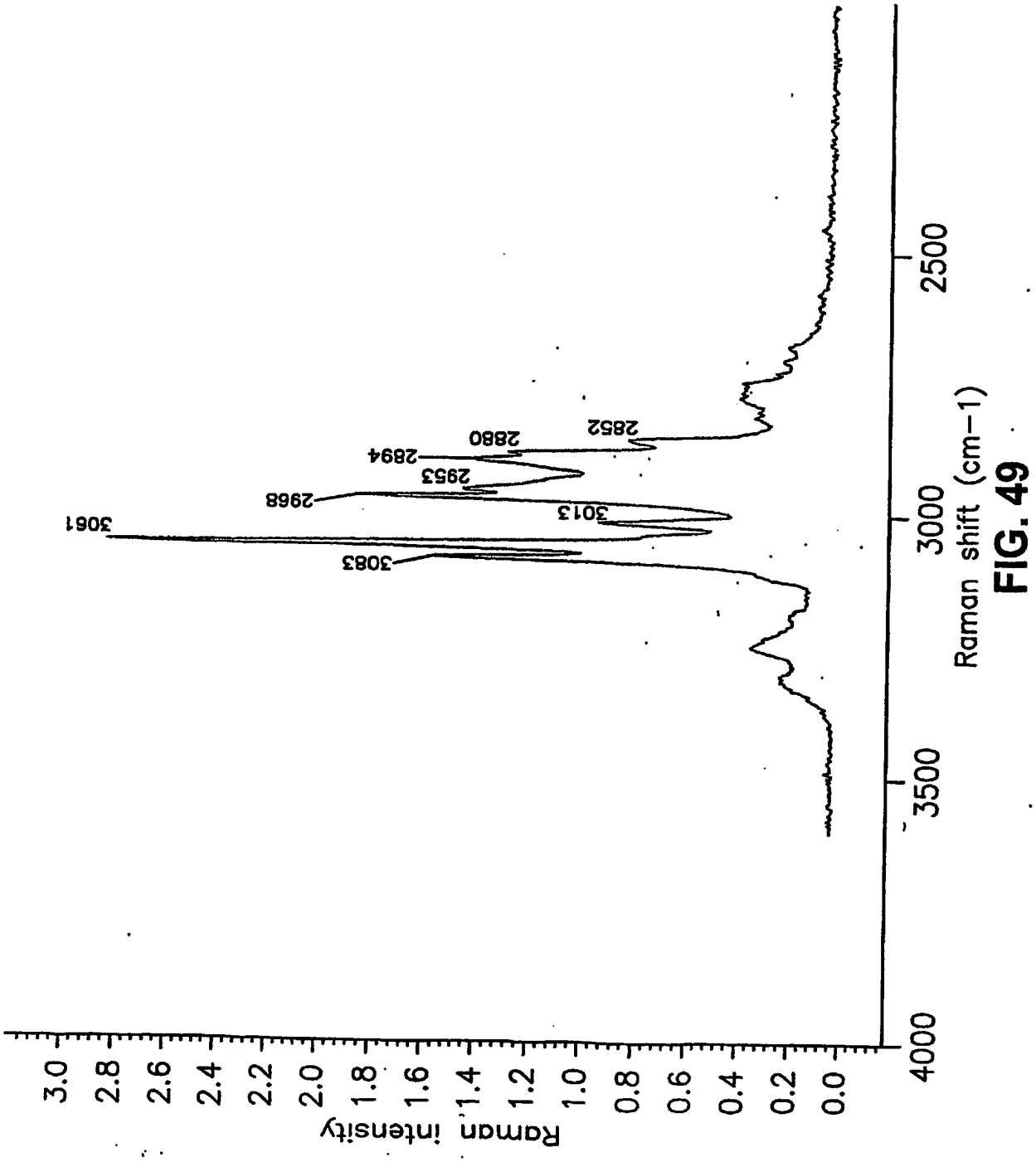

Raman intensity
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
4000
3500
3000
2500
Raman shift (cm−1)
3061
3083
3013
2968
2953
2894
2880
2852

FIG. 49

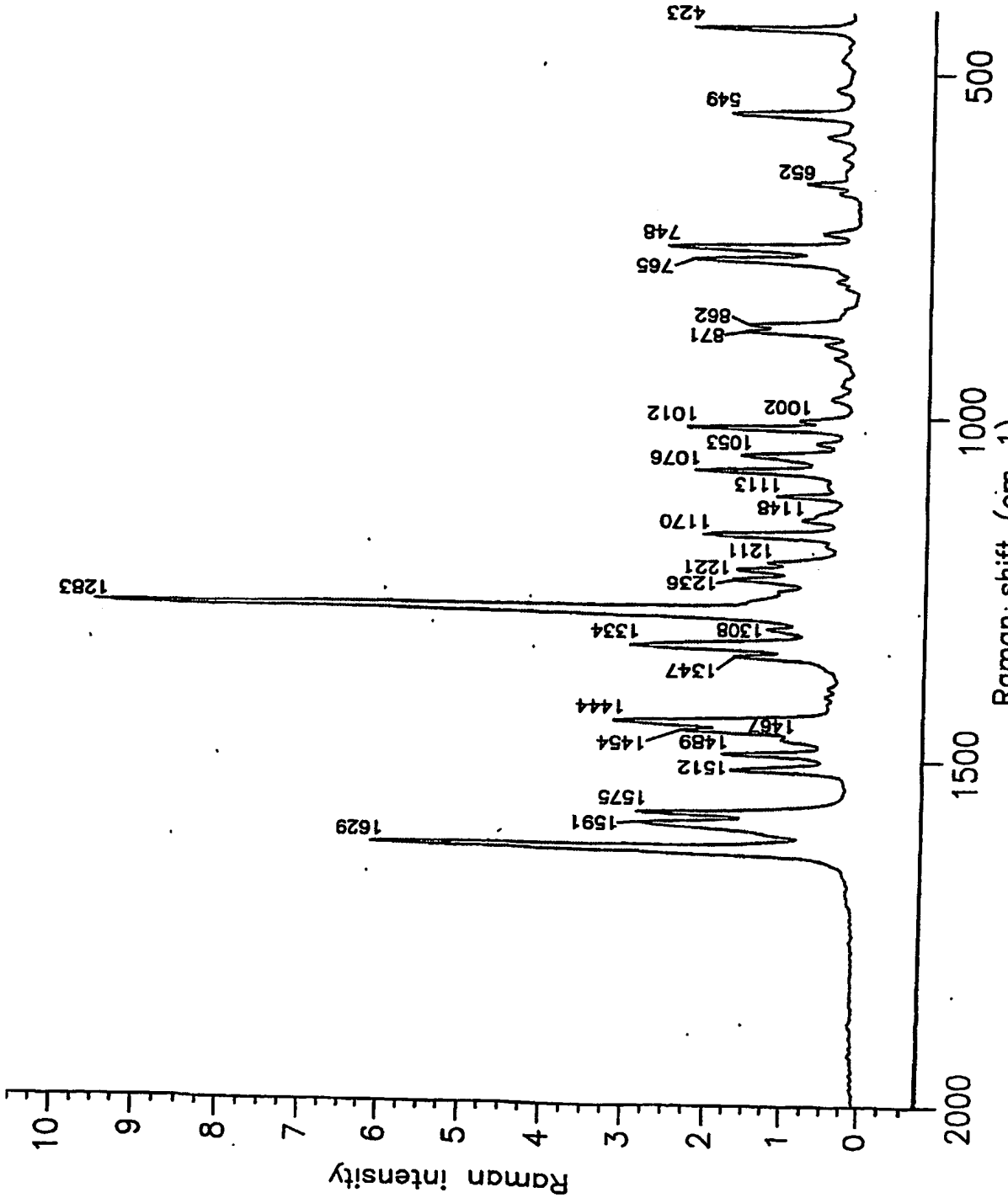

Raman intensity
0
1
2
3
4
5
6
7
8
9
10
2000
1500
1000
500
Raman shift (cm−1)
423
549
652
748
765
862
871
1002
1012
1053
1076
1113
1148
1170
1211
1221
1236
1283
1308
1334
1347
1444
1457
1489
1454
1512
1575
1591
1629

FIG. 50

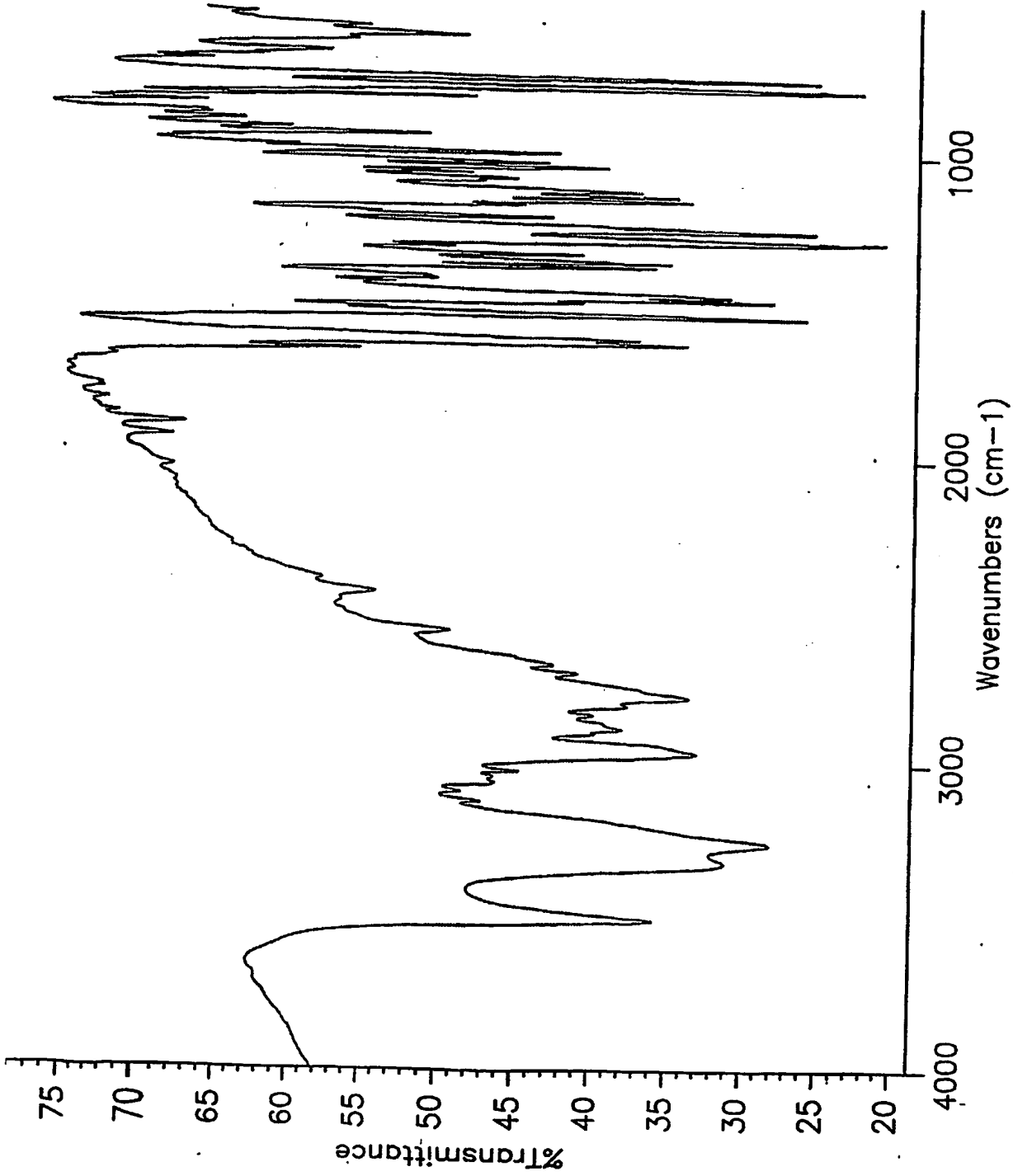

%Transmittance
75
70
65
60
55
50
45
40
35
30
25
20
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 51

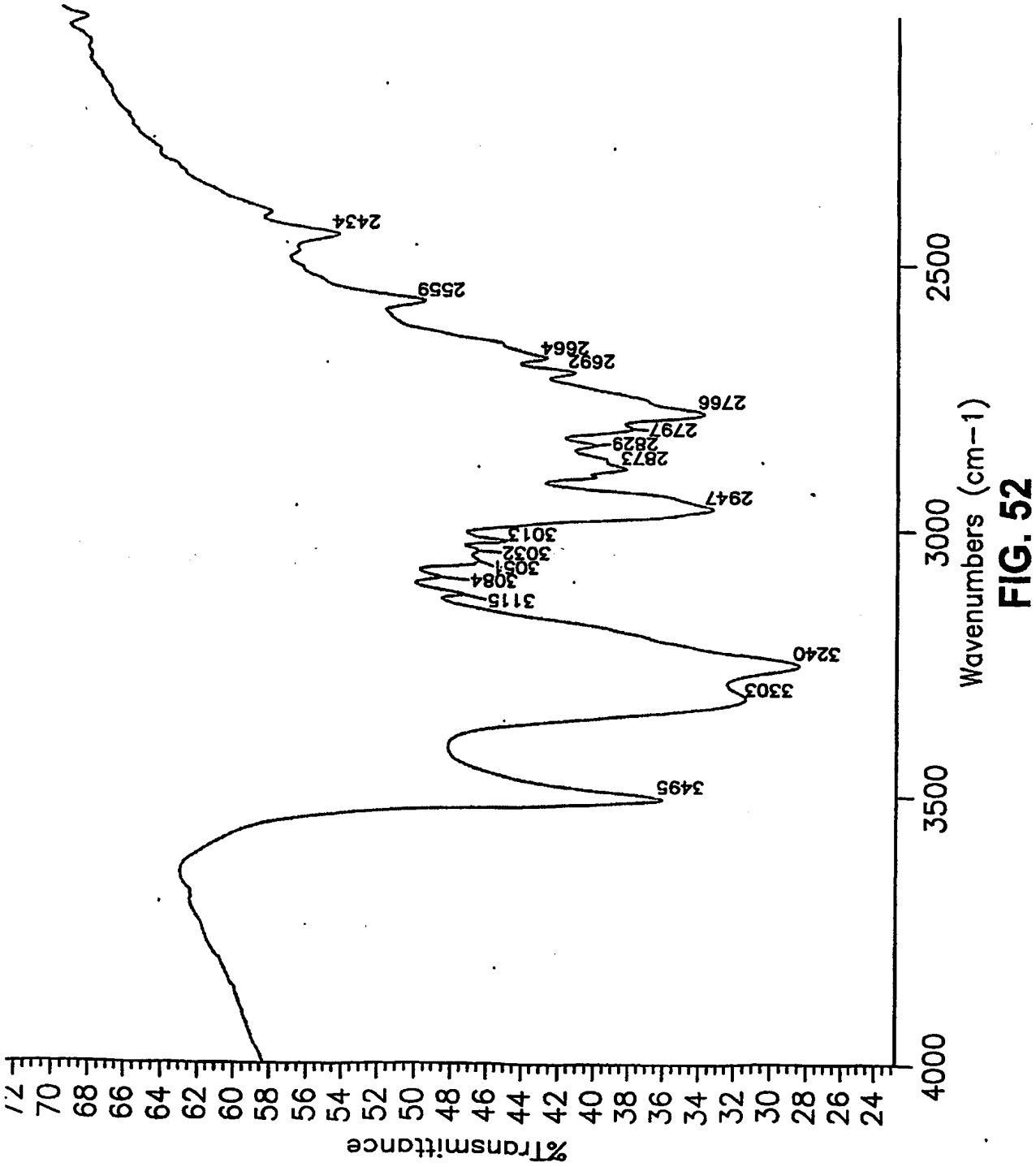

%Transmittance
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
4000
3500
3000
2500
Wavenumbers (cm-1)
3495
3303
3240
3115
3084
3051
3032
3013
2947
2873
2829
2797
2766
2692
2664
2559
2434

FIG. 52

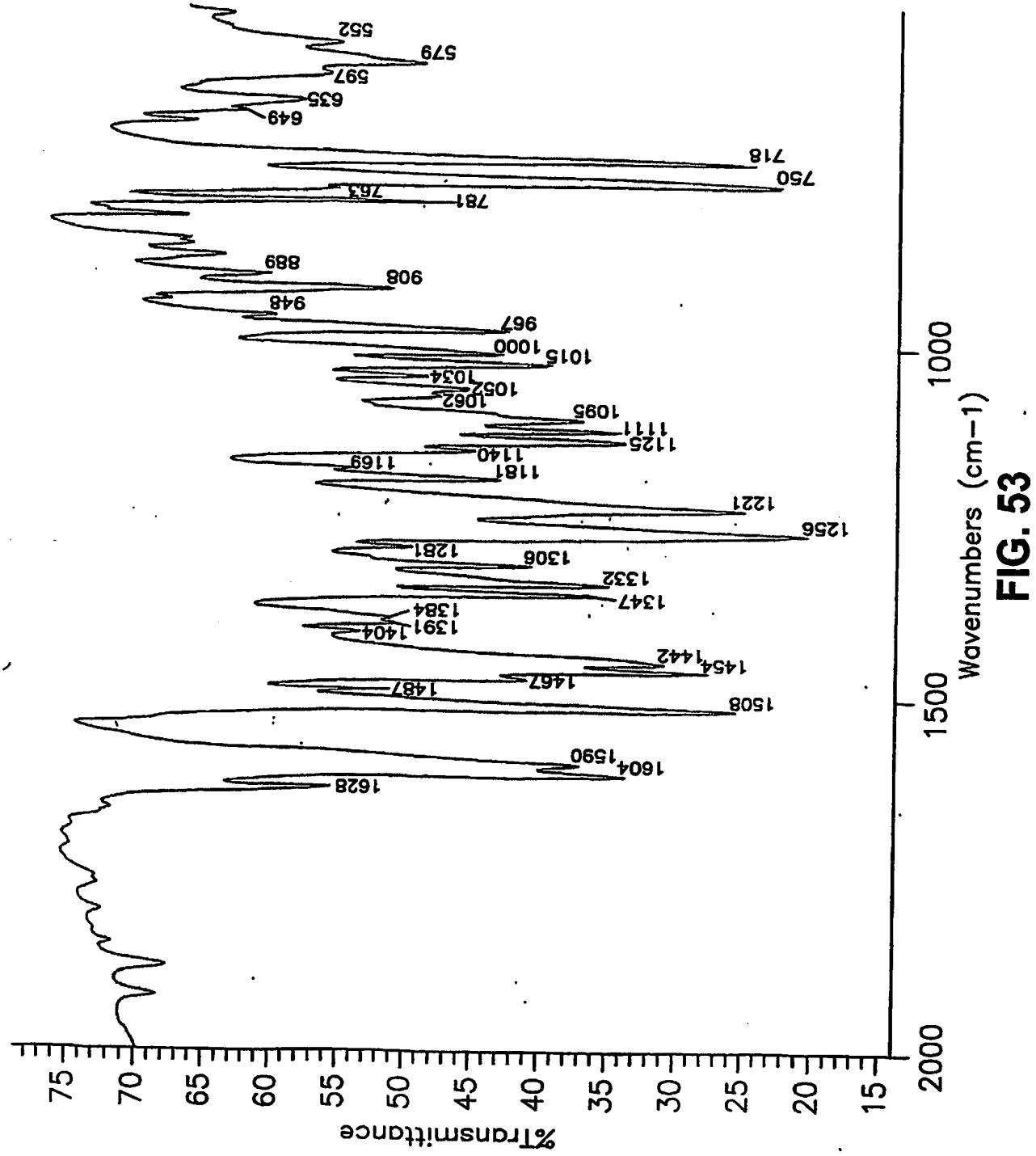

%Transmittance
75
70
65
60
55
50
45
40
35
30
25
20
15
2000
1500
1000
Wavenumbers (cm−1)
552
579
597
635
649
718
750
763
781
889
908
948
967
1000
1015
1034
1052
1062
1095
1111
1125
1140
1169
1181
1221
1256
1281
1306
1332
1347
1384
1391
1404
1442
1454
1467
1487
1508
1590
1604
1628

FIG. 53

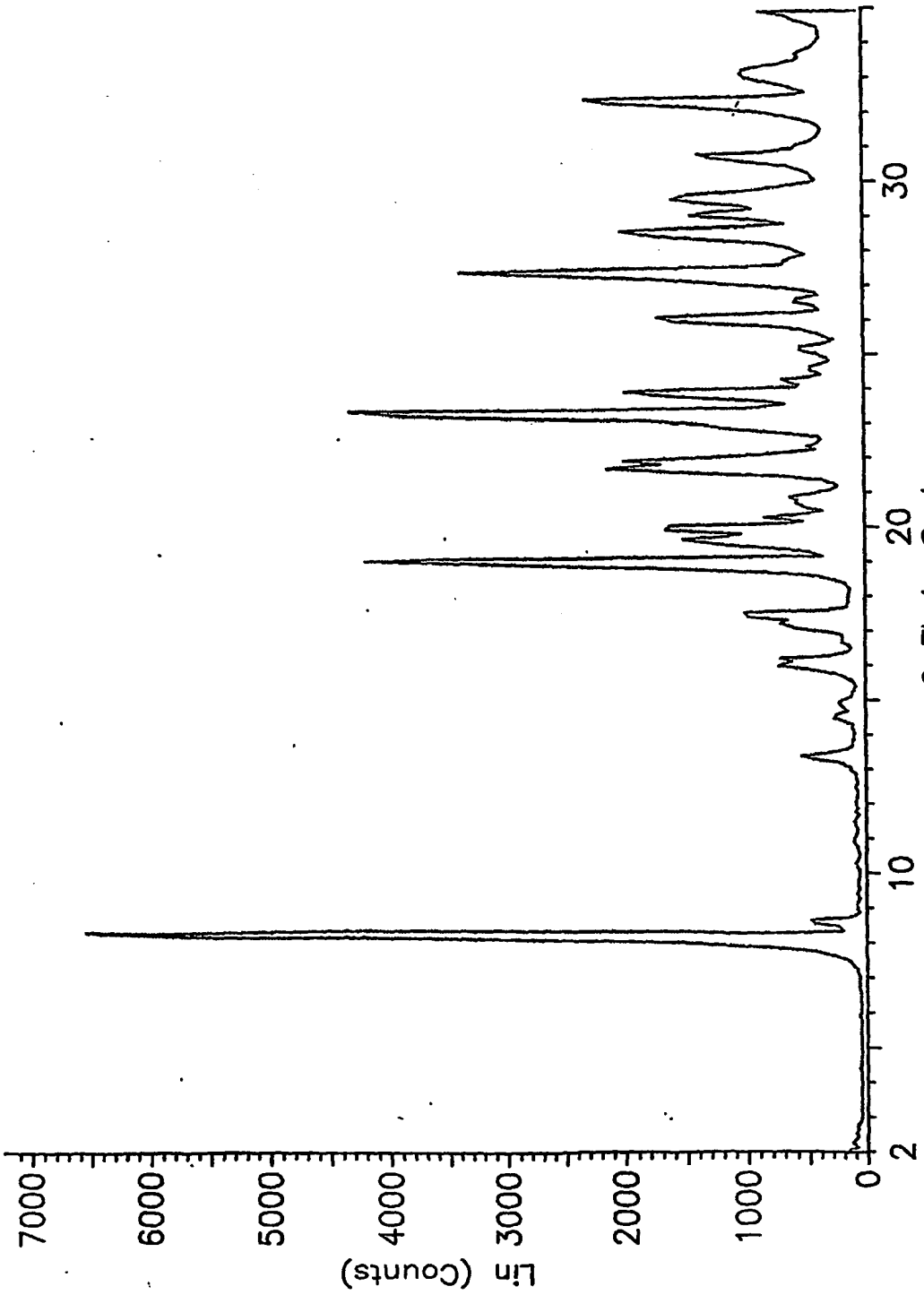

Lin (Counts)
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
2-Theta-Scale

FIG. 54

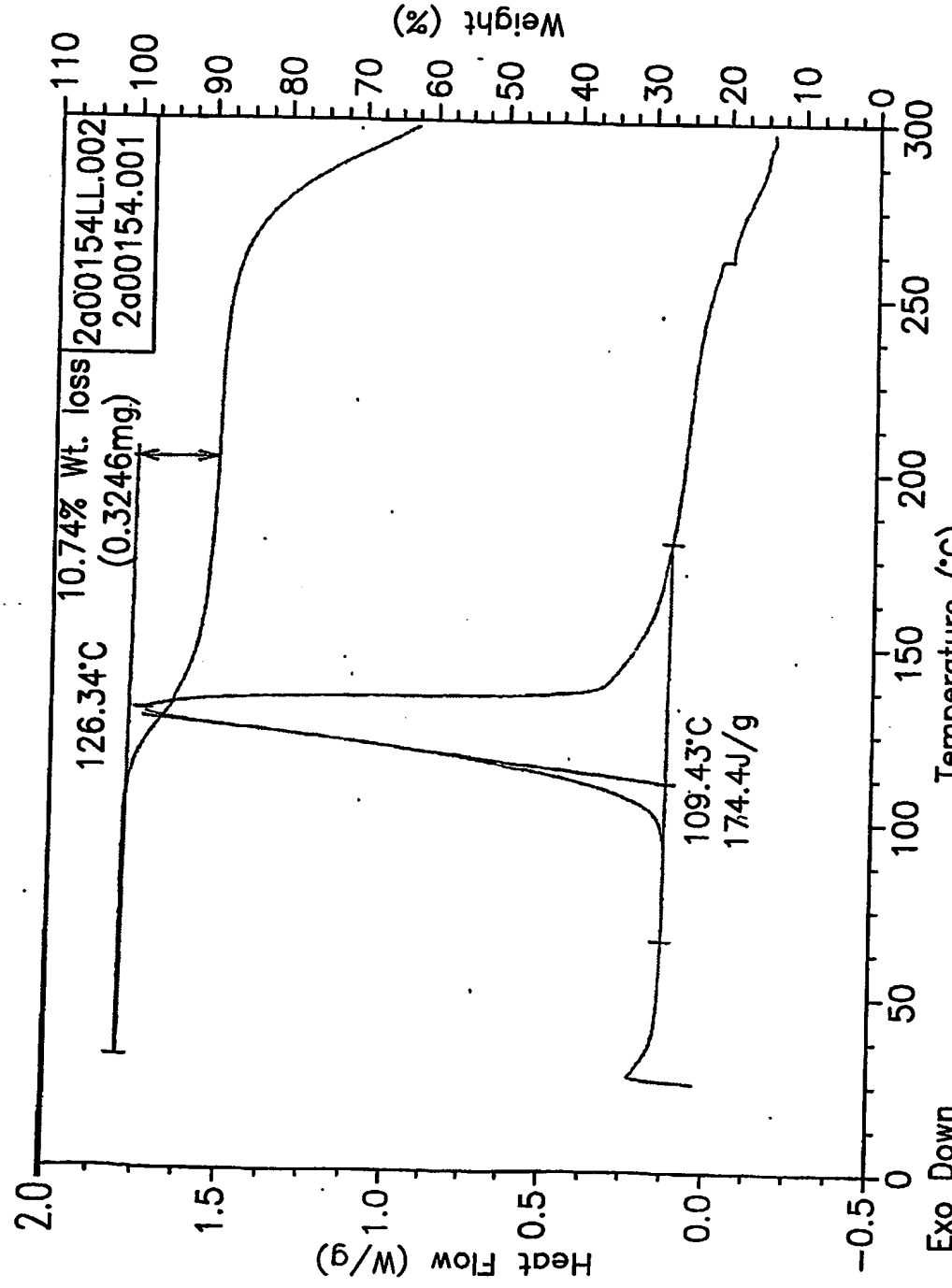

Weight (%)
110
100
90
80
70
60
50
40
30
20
10
0
2a00154LL.002
2a00154.001
10.74% Wt. loss
(0.3246mg)
126.34°C
109.43°C
174.4J/g
Heat Flow (W/g)
2.0
1.5
1.0
0.5
0.0
-0.5
Exo Down
0
50
100
150
200
250
300
Temperature (°C)

FIG. 55

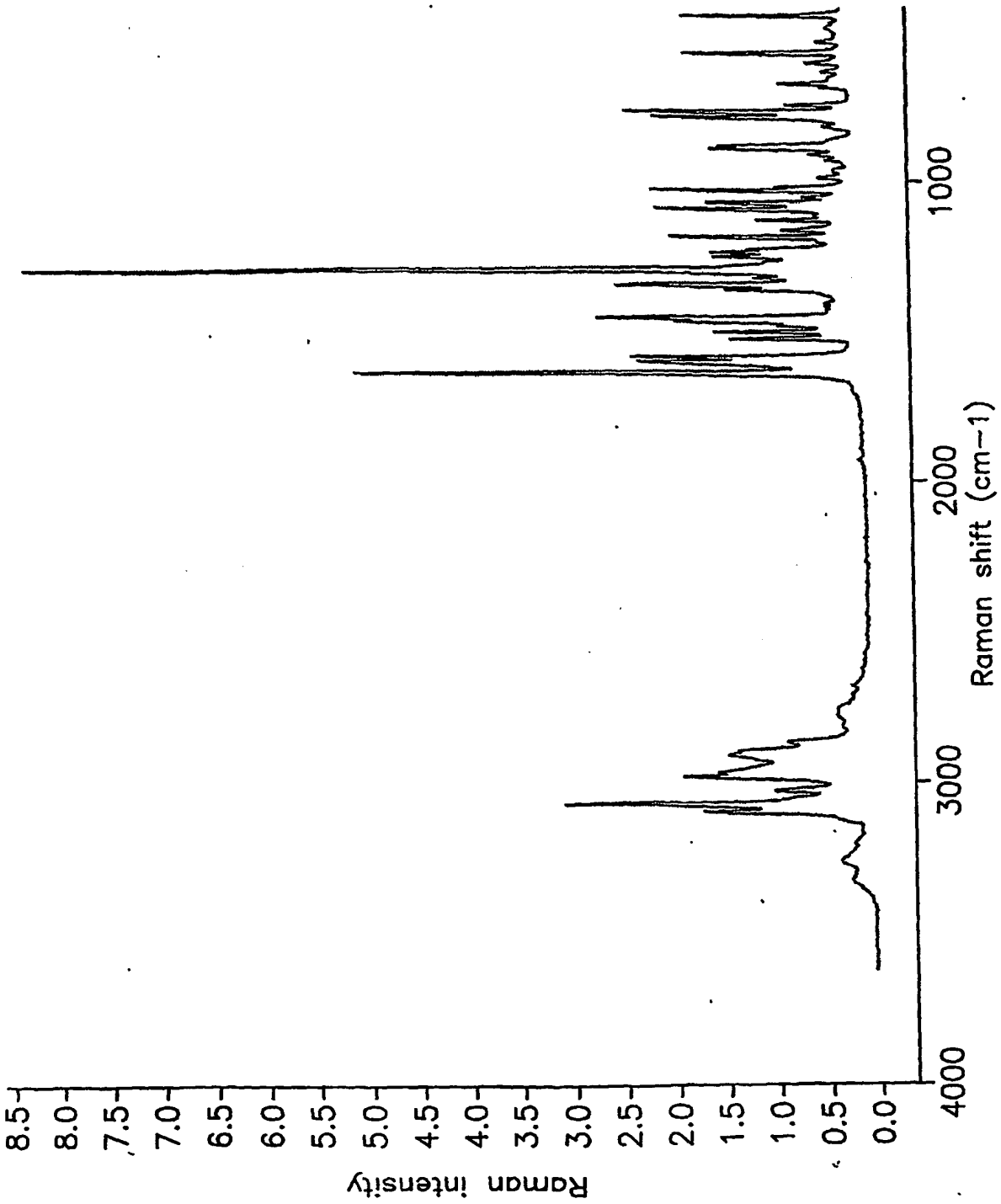

Raman intensity
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4000
3000
2000
1000
Raman shift (cm−1)

FIG. 56

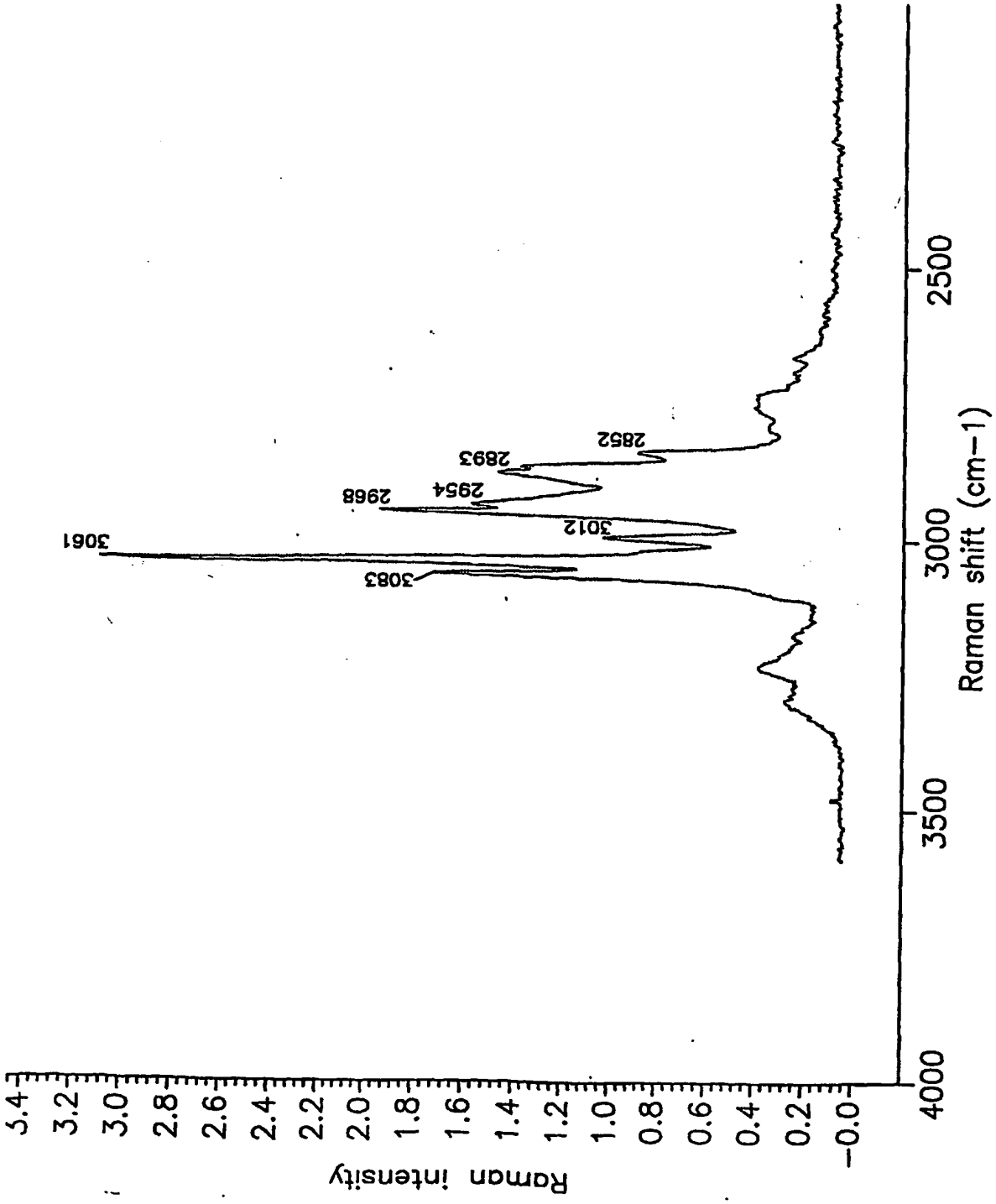

Raman intensity
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
-0.0
4000
3500
3000
2500
Raman shift (cm-1)
3061
3083
3012
2968
2954
2893
2852

FIG. 57

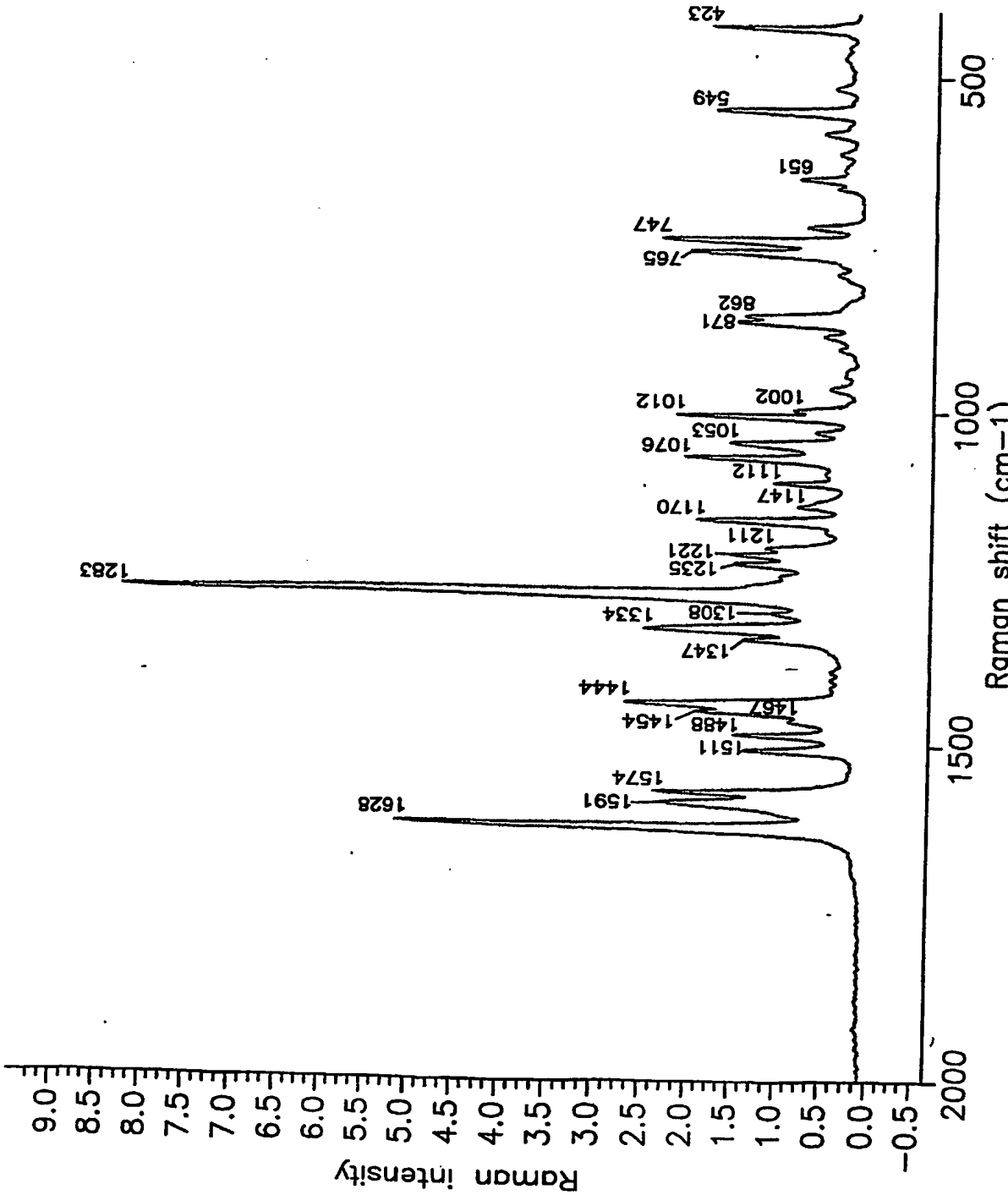

Raman intensity
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
2000
1500
1000
500
Raman shift (cm−1)
423
549
651
747
765
862
871
1002
1012
1053
1076
1112
1147
1170
1211
1221
1235
1283
1308
1334
1347
1444
1467
1488
1454
1511
1574
1591
1628

FIG. 58

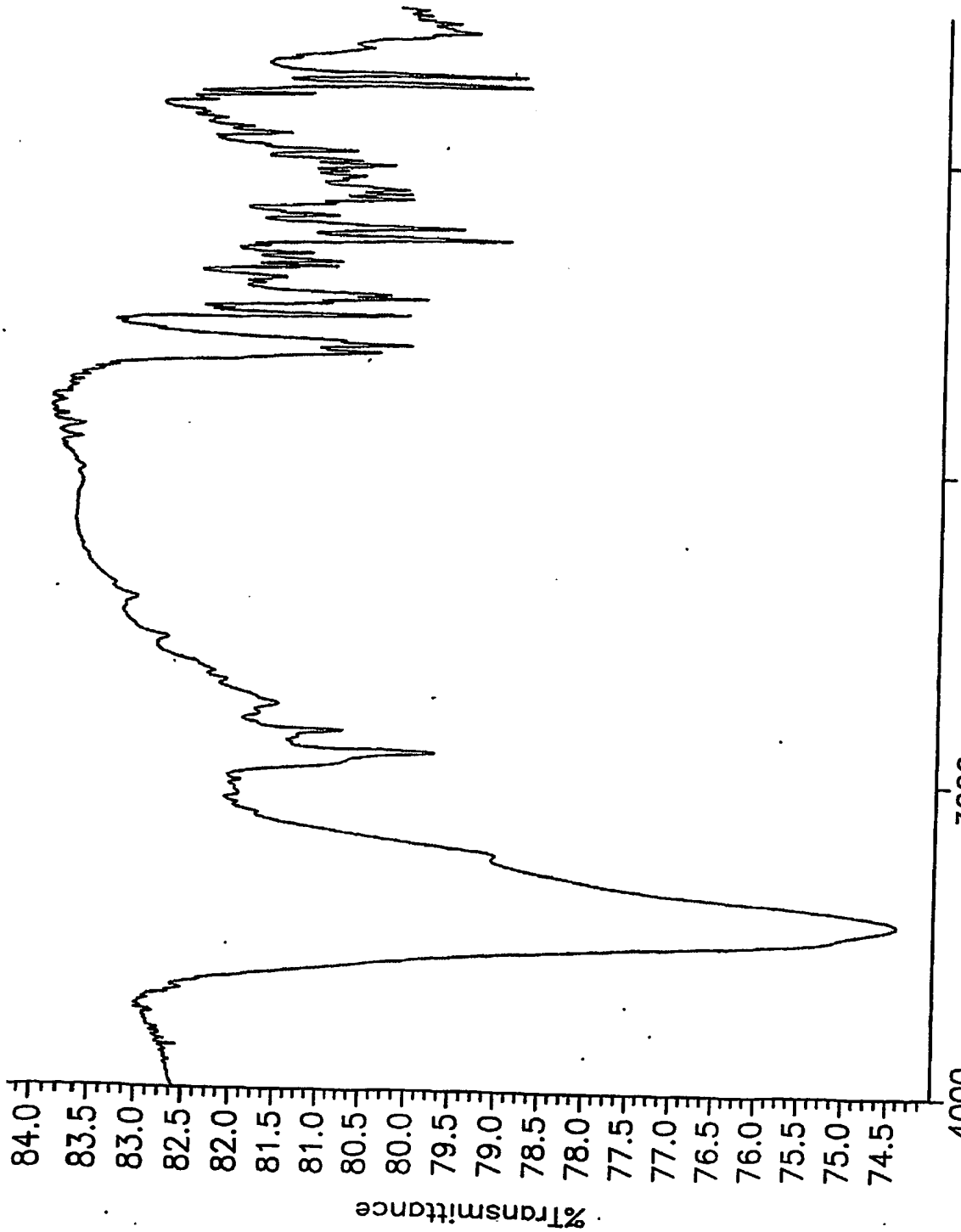

%Transmittance
84.0
83.5
83.0
82.5
82.0
81.5
81.0
80.5
80.0
79.5
79.0
78.5
78.0
77.5
77.0
76.5
76.0
75.5
75.0
74.5
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 59

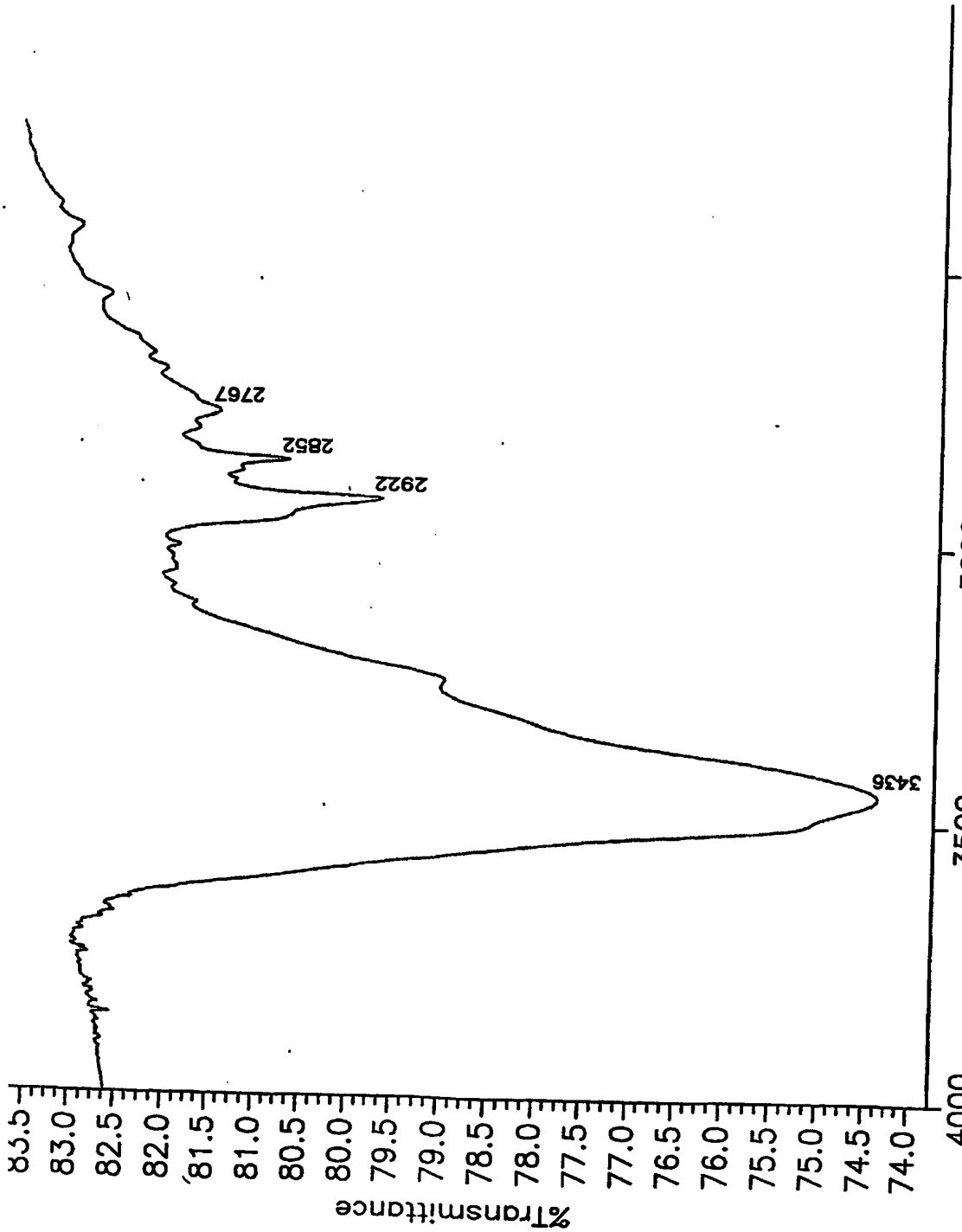

%Transmittance
83.5
83.0
82.5
82.0
81.5
81.0
80.5
80.0
79.5
79.0
78.5
78.0
77.5
77.0
76.5
76.0
75.5
75.0
74.5
74.0
4000
3500
3000
2500
Wavenumbers (cm−1)
3436
2922
2852
2767

FIG. 60

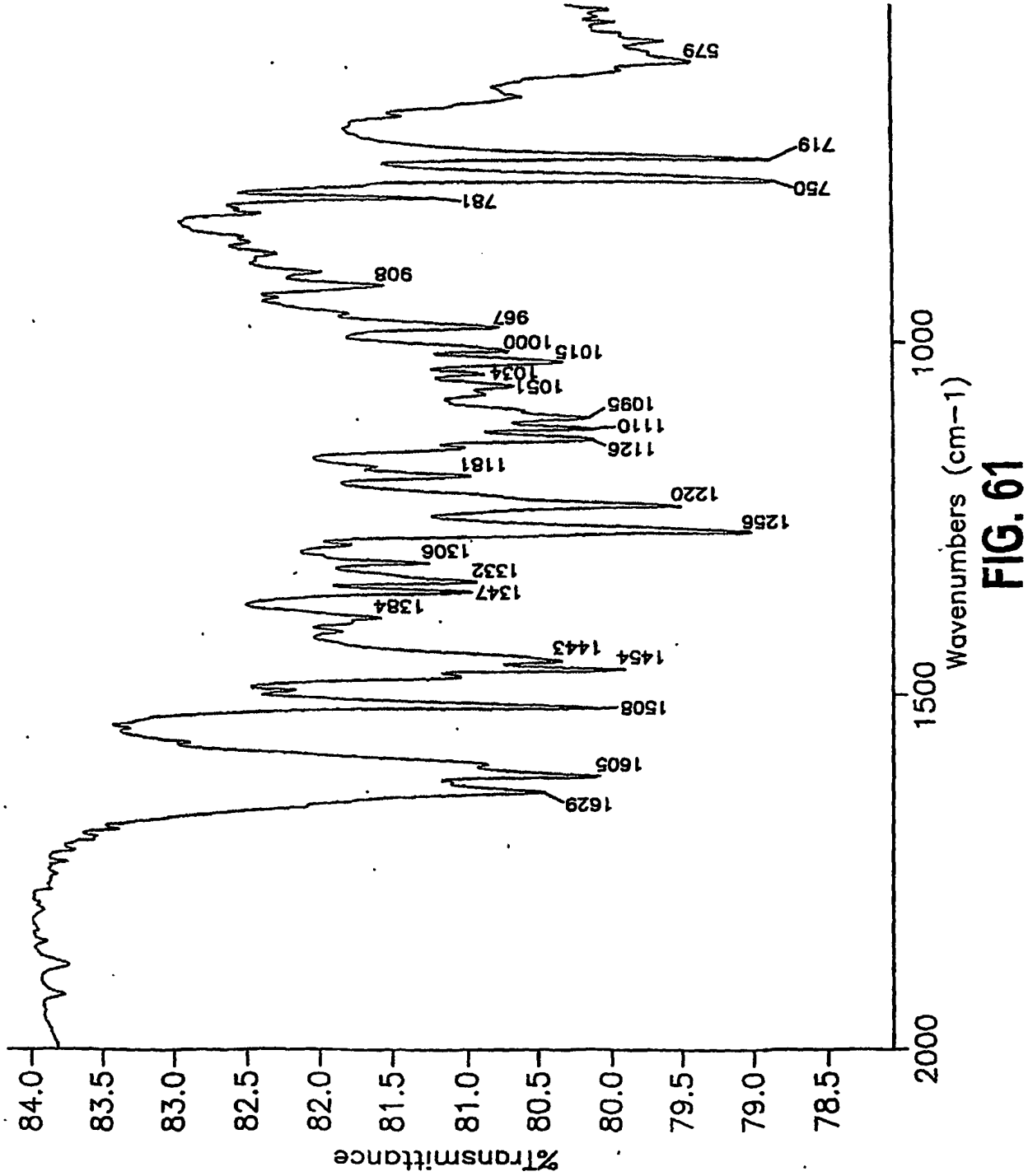

%Transmittance
84.0
83.5
83.0
82.5
82.0
81.5
81.0
80.5
80.0
79.5
79.0
78.5
2000
1500
1000
Wavenumbers (cm−1)
579
719
750
781
908
967
1000
1015
1034
1051
1095
1110
1126
1181
1220
1256
1306
1332
1347
1384
1443
1454
1508
1605
1629

FIG. 61

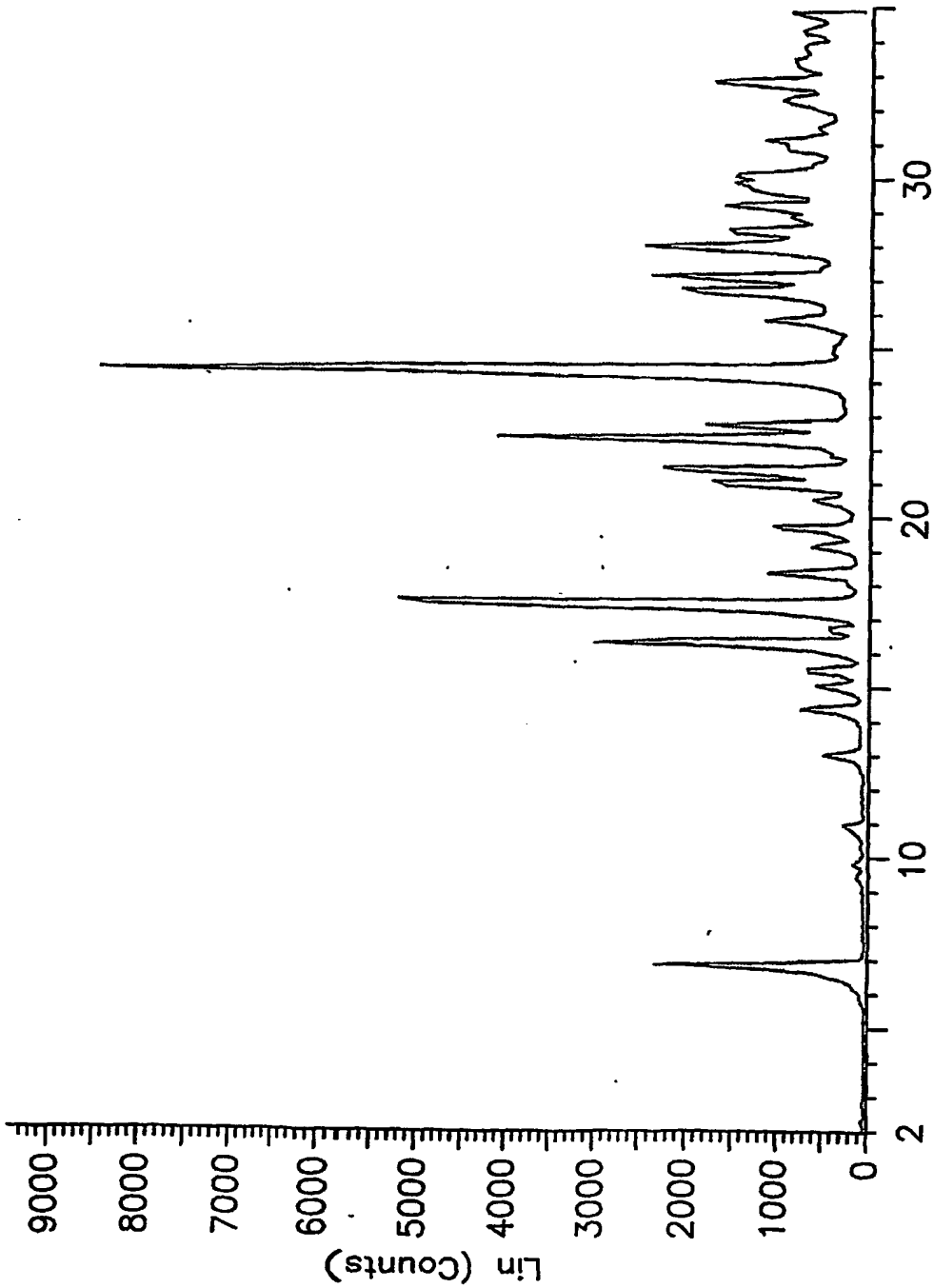

Lin (Counts)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2
10
20
30
2-Theta-Scale

FIG. 62

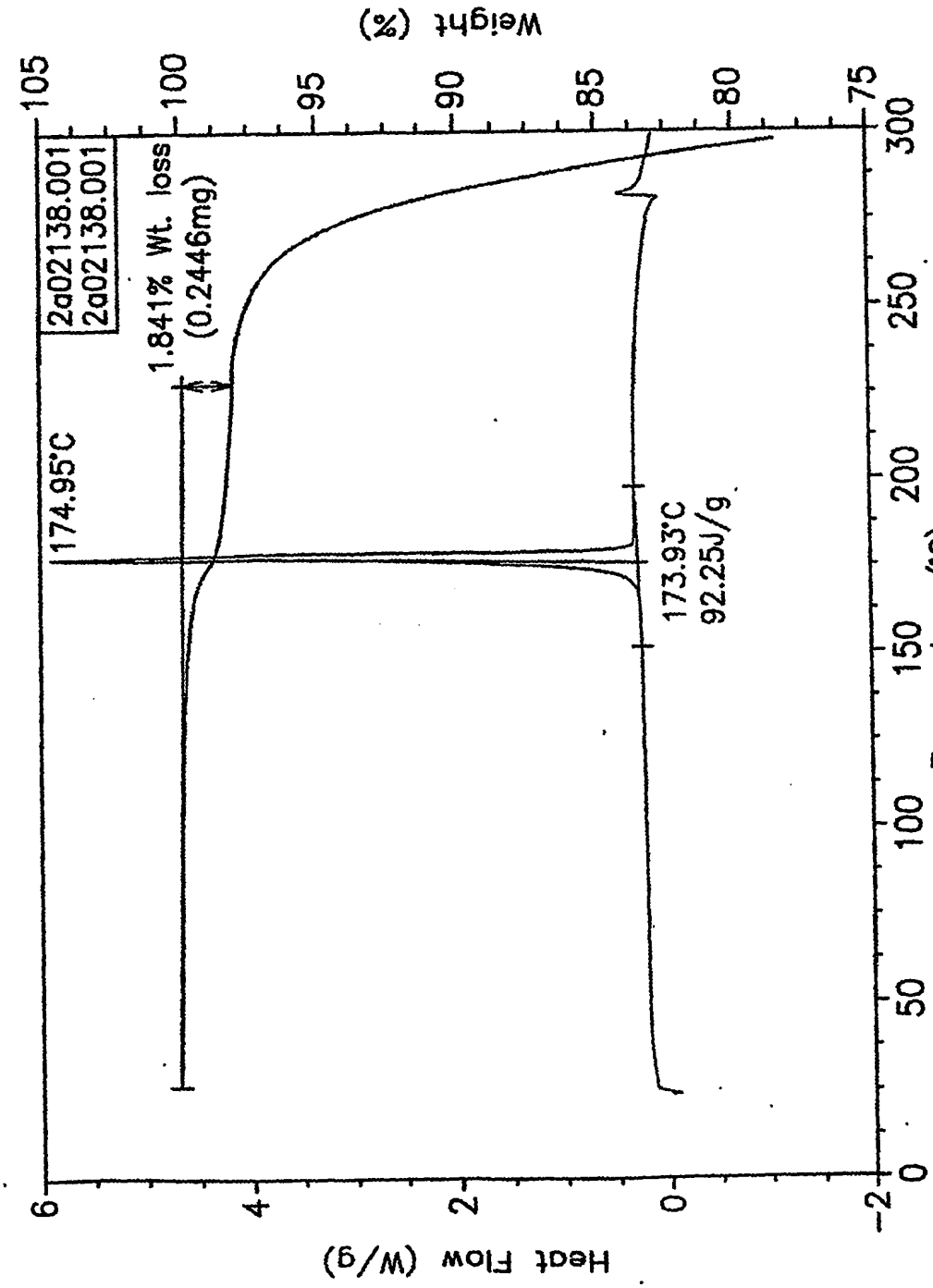

Weight (%)
105
100
95
90
85
80
75
2a02138.001
2a02138.001
1.841% Wt. loss
(0.2446mg)
174.95°C
173.93°C
92.25J/g
Heat Flow (W/g)
6
4
2
0
-2
Exo Down
0
50
100
150
200
250
300
Temperature (°C)

FIG. 63

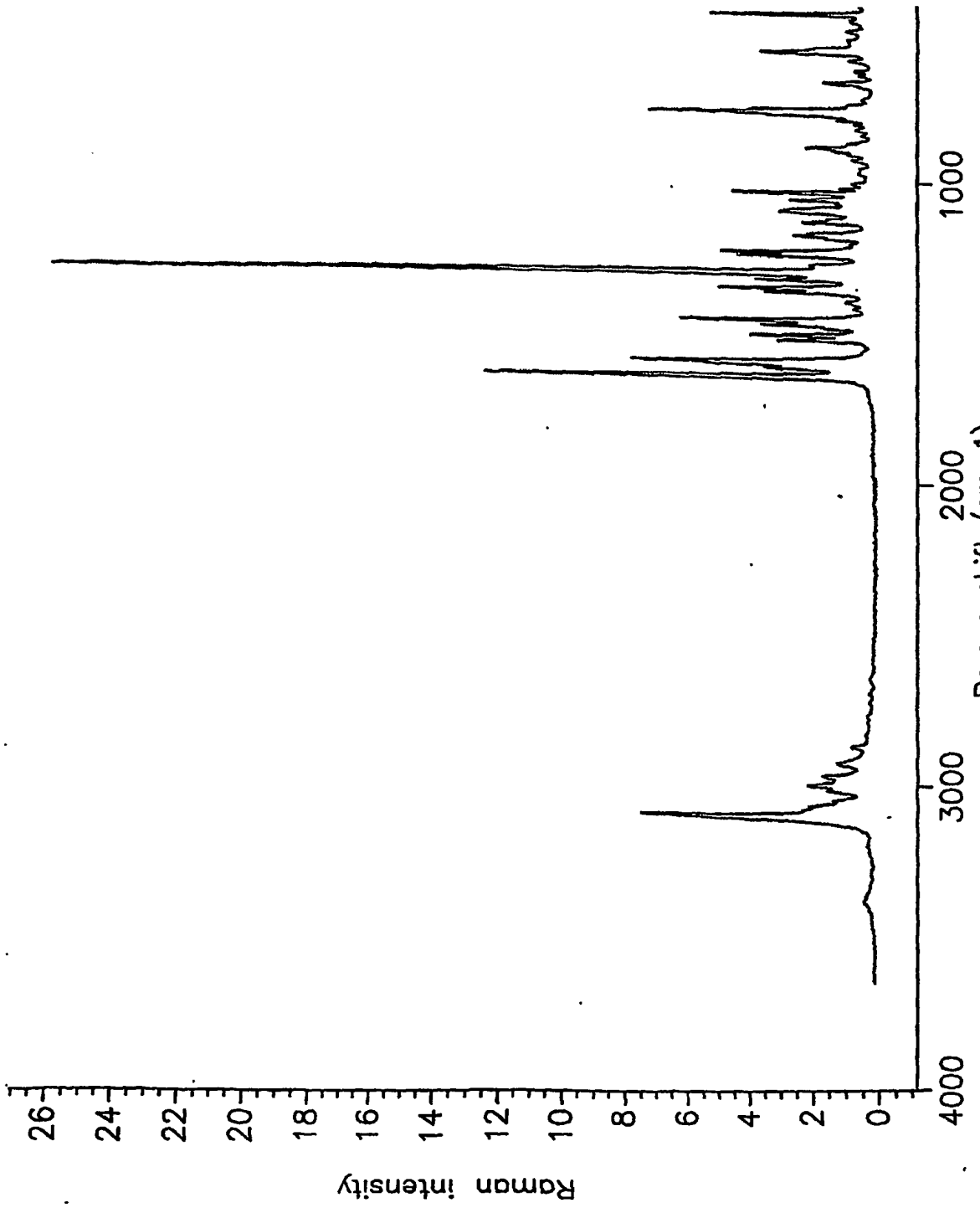

Raman intensity
0
2
4
6
8
10
12
14
16
18
20
22
24
26
4000
3000
2000
1000
Raman shift (cm−1)

FIG. 64

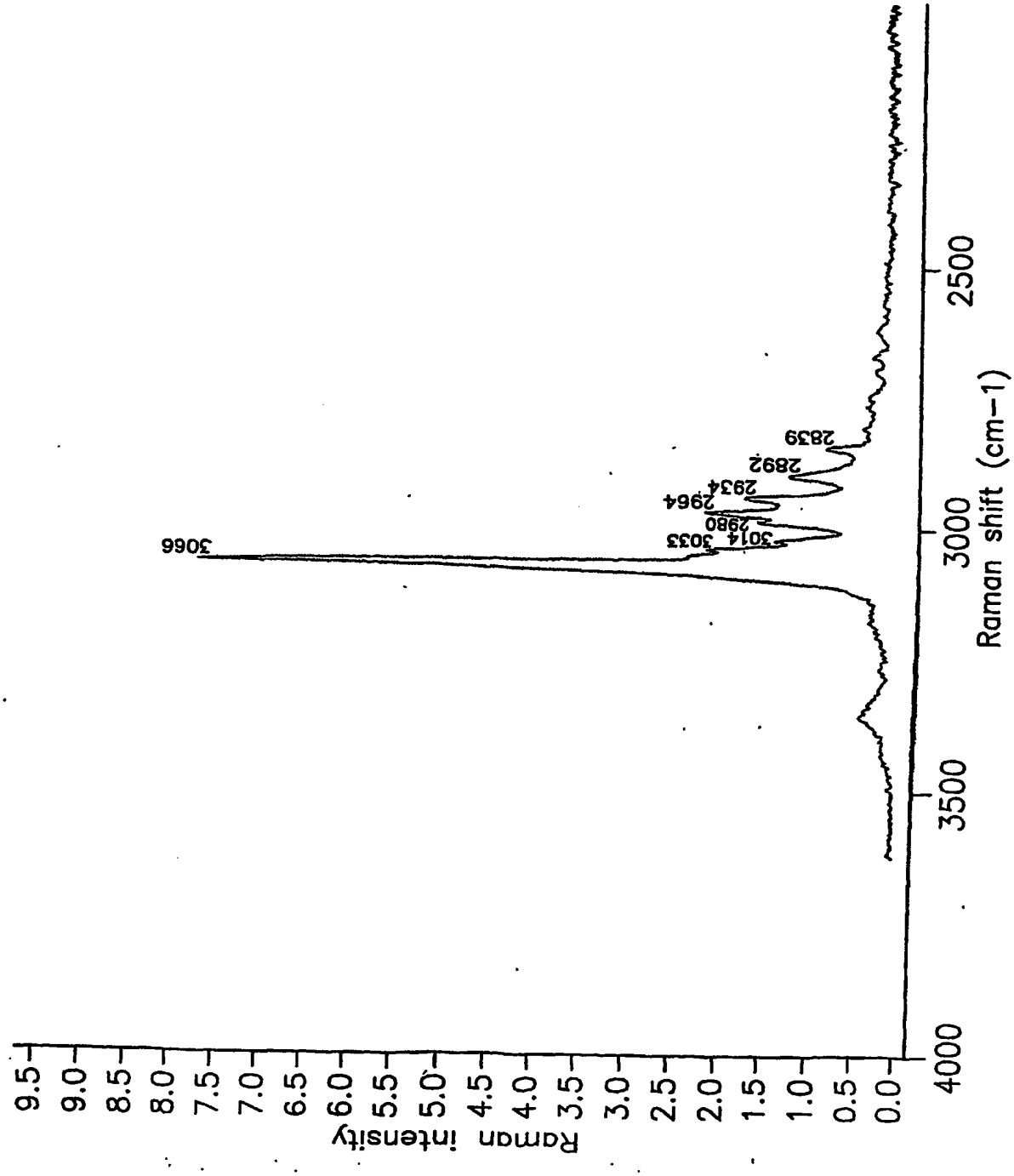

Raman intensity
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4000
3500
3000
2500
Raman shift (cm−1)
3066
3014
3033
2980
2964
2934
2892
2839

FIG. 65

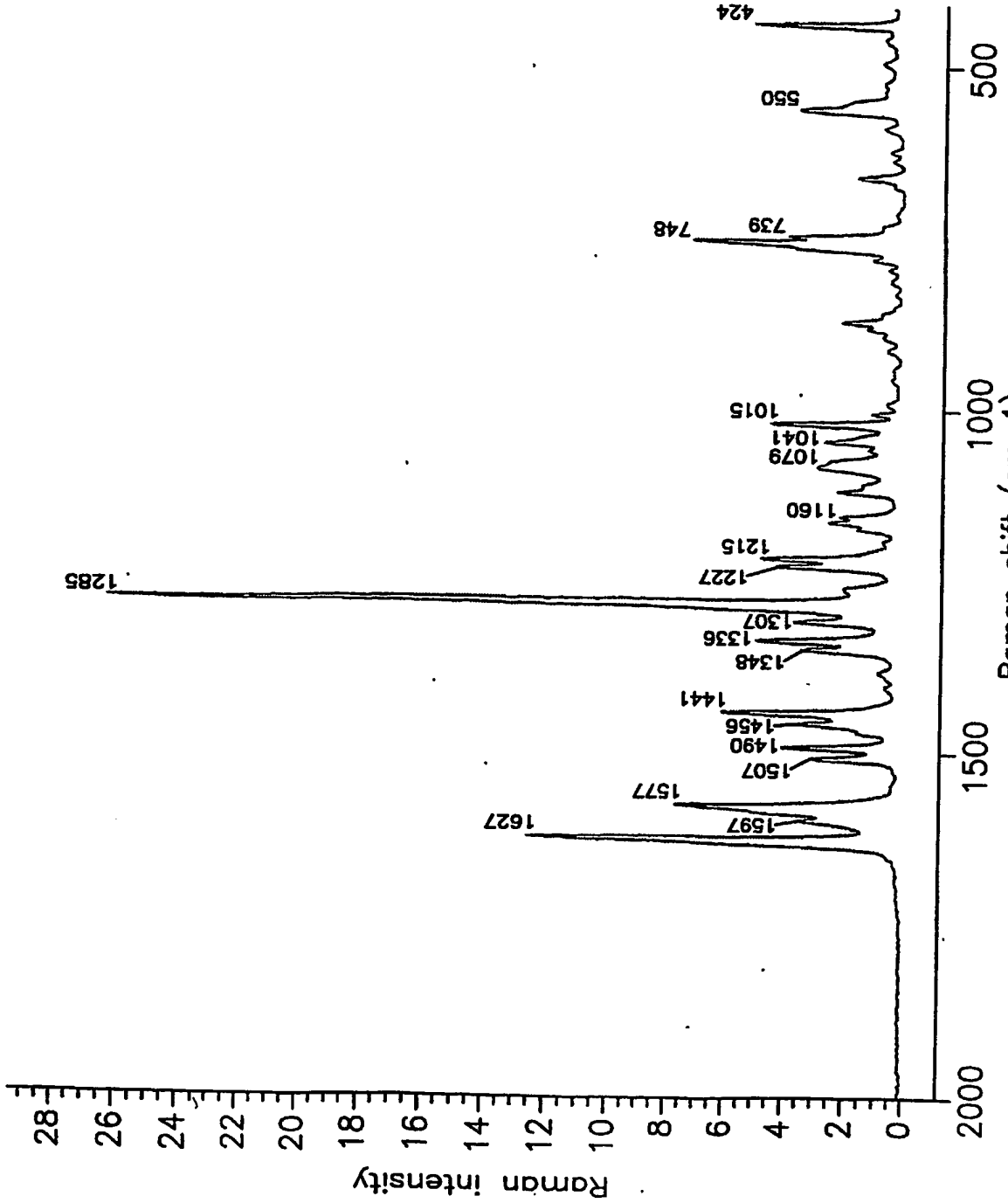

Raman intensity
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
2000
1500
1000
500
Raman shift (cm−1)
424
550
739
748
1015
1041
1079
1160
1215
1227
1285
1307
1336
1348
1441
1456
1490
1507
1577
1597
1627

FIG. 66

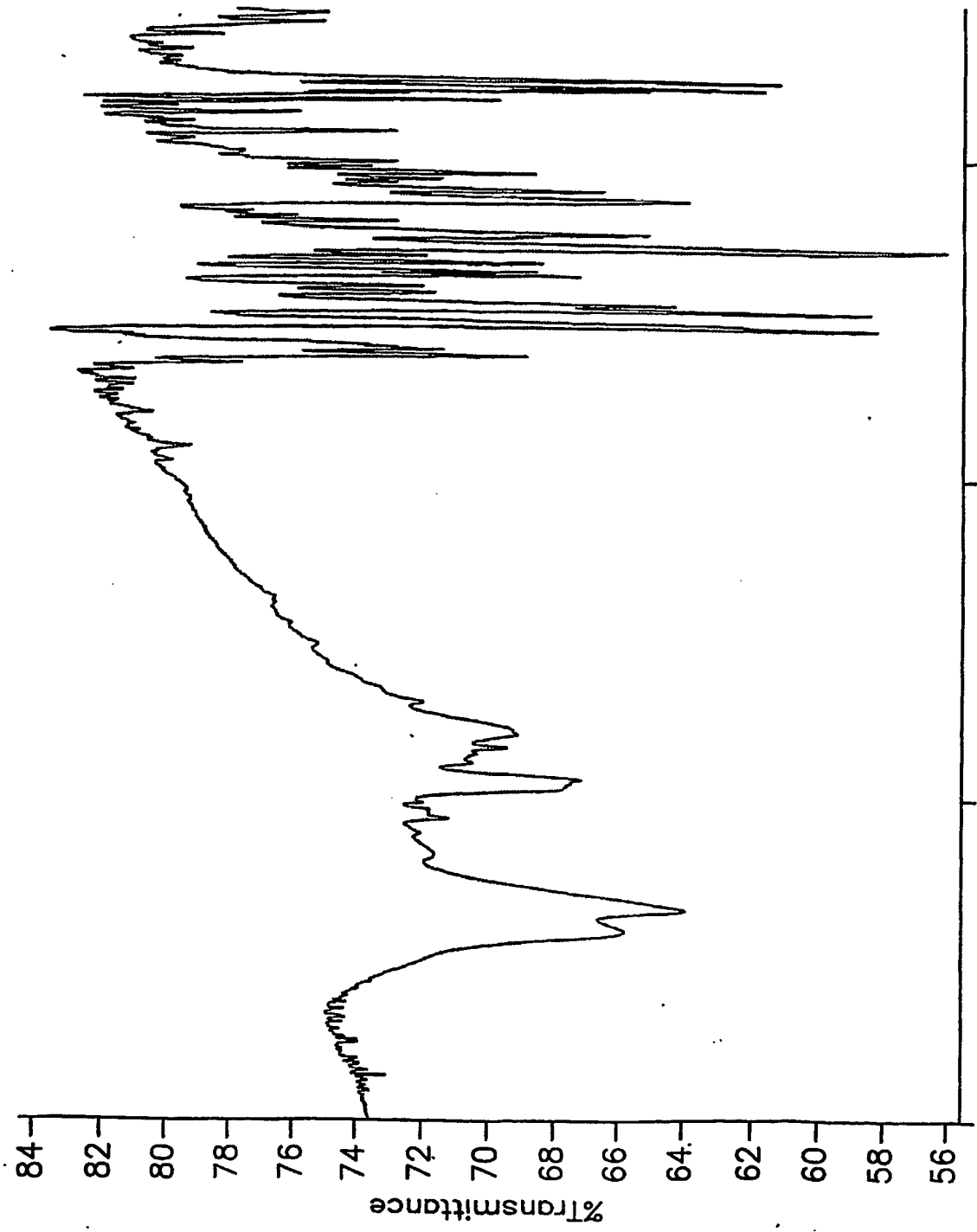

%Transmittance
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
4000
3000
2000
1000
Wavenumbers (cm−1)

FIG. 67

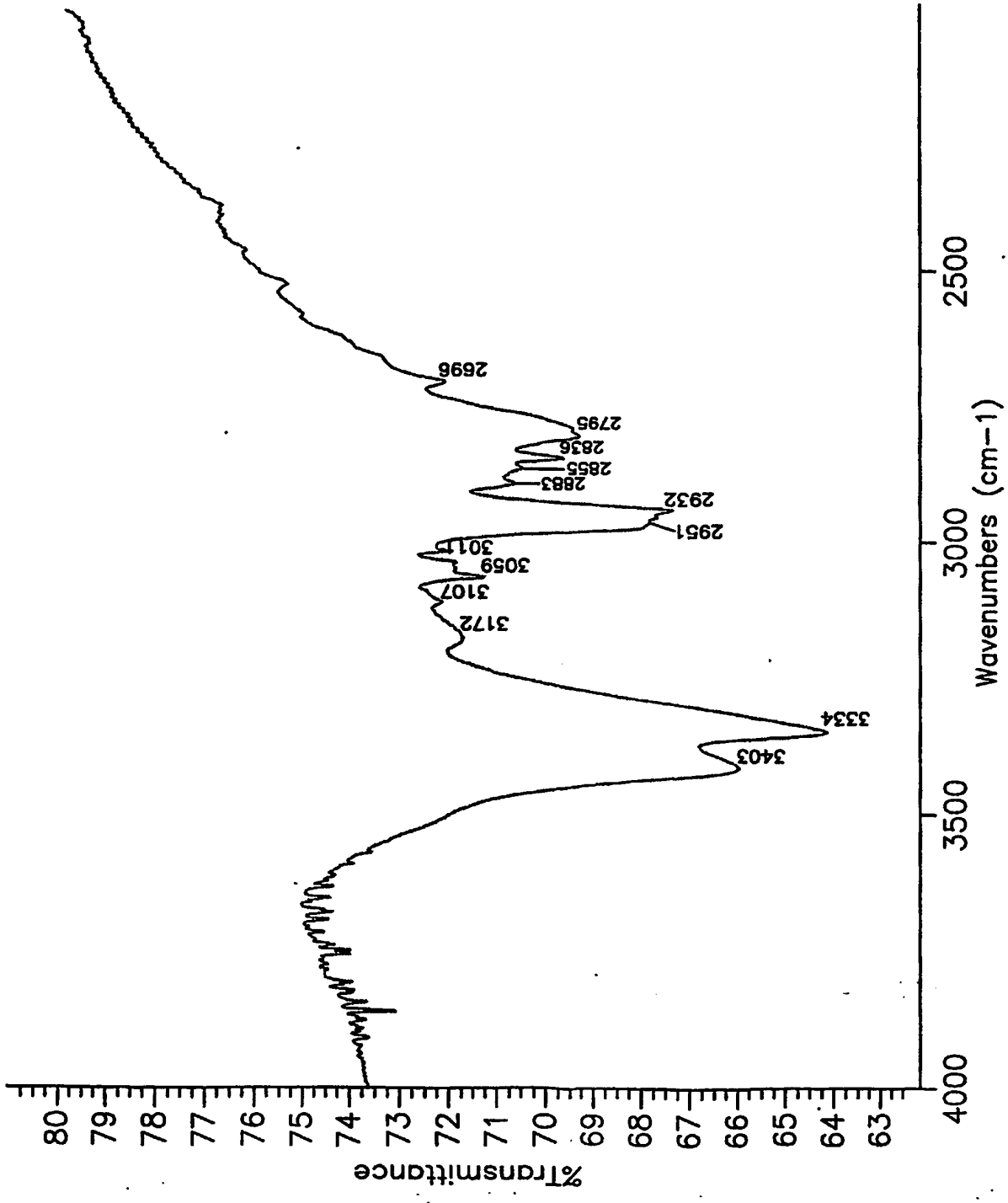

%Transmittance
80
79
78
77
76
75
74
73
72
71
70
69
68
67
66
65
64
63
4000
3500
3000
2500
Wavenumbers (cm−1)
3334
3403
3172
3107
3059
3015
2951
2932
2883
2855
2836
2795
2696

FIG. 68

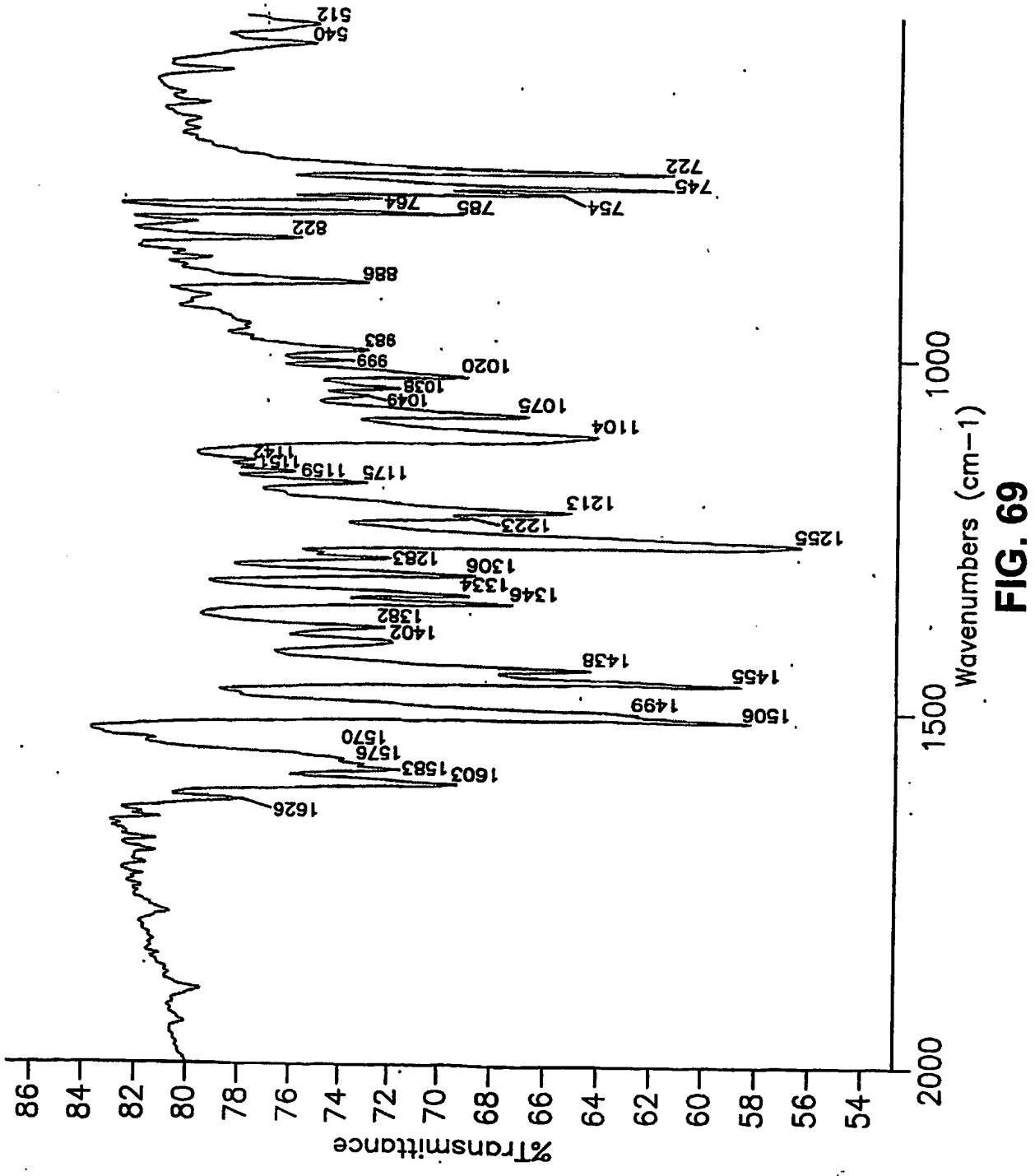

%Transmittance
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
2000
1500
1000
Wavenumbers (cm−1)
512
540
722
745
754
764
785
822
886
983
999
1020
1038
1049
1075
1104
1142
1151
1159
1175
1213
1223
1255
1283
1306
1334
1346
1382
1402
1438
1455
1499
1506
1570
1576
1583
1603
1626

FIG. 69

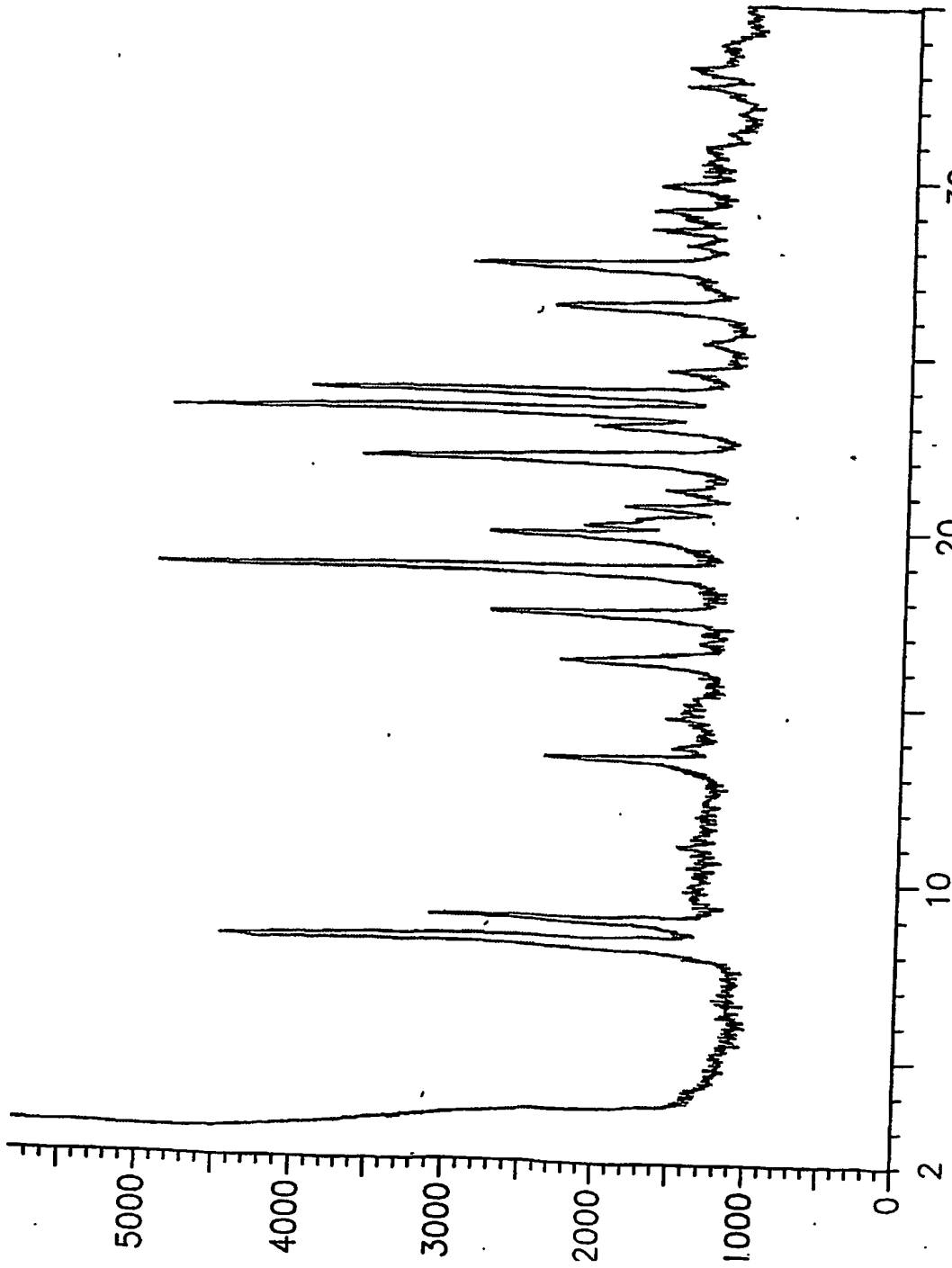


FIG. 70

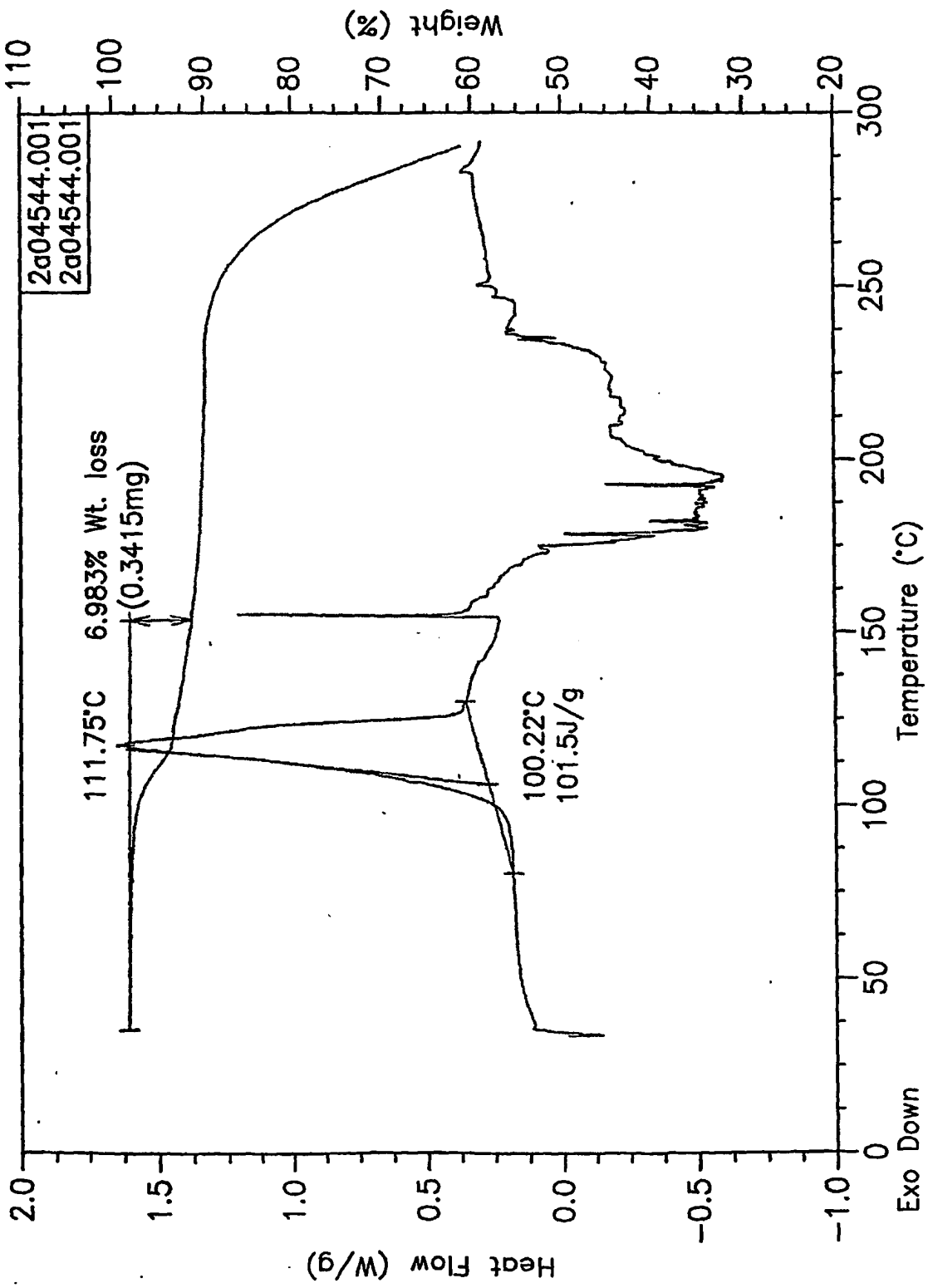

Weight (%)
110
100
90
80
70
60
50
40
30
20
2a04544.001
2a04544.001
6.983% Wt. loss
(0.3415mg)
111.75°C
100.22°C
101.5J/g
Heat Flow (W/g)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
Exo Down
0
50
100
150
200
250
300
Temperature (°C)

FIG. 71

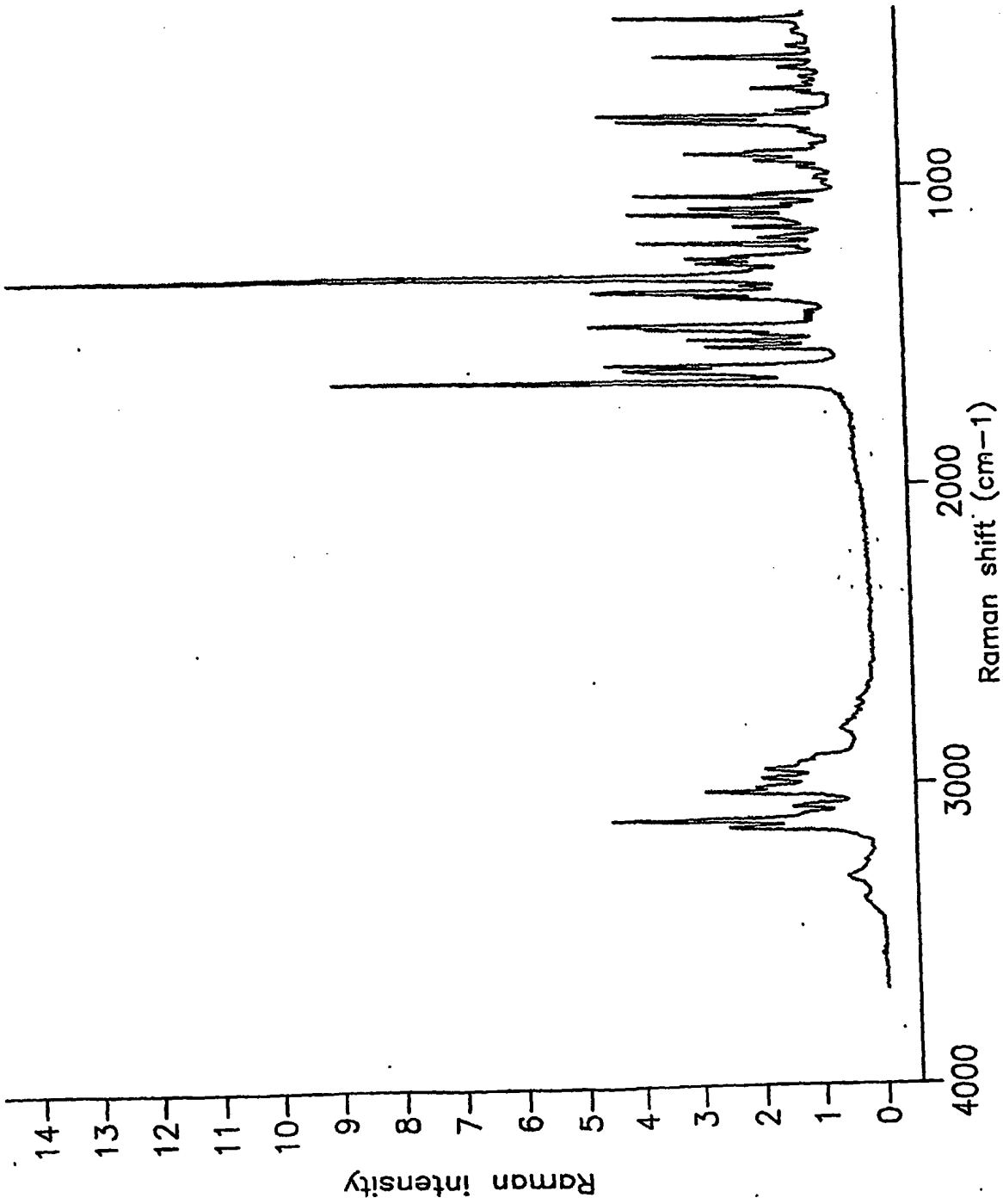

Raman intensity
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
4000
3000
2000
1000
Raman shift (cm−1)

FIG. 72

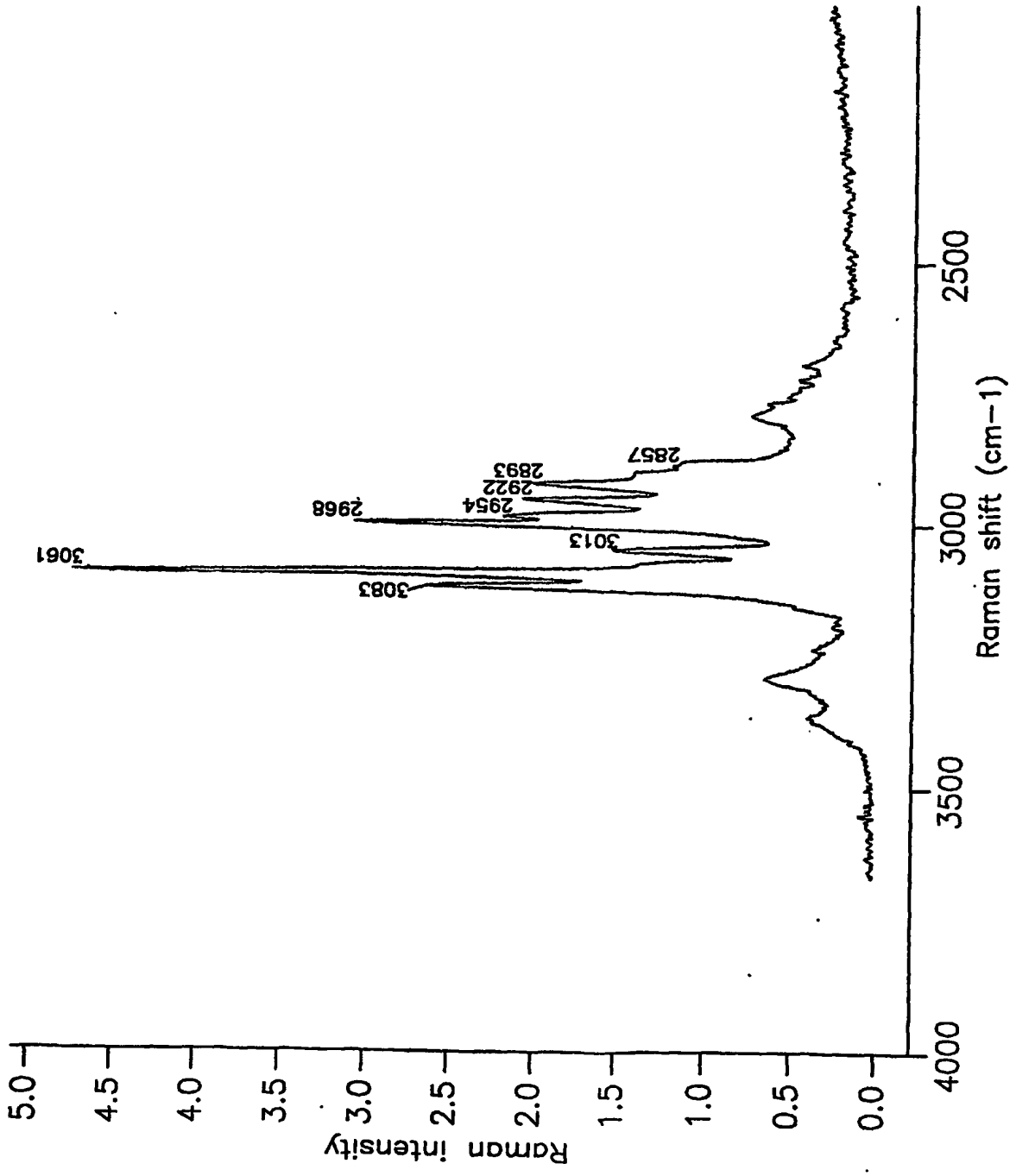

Raman intensity
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4000
3500
3000
2500
Raman shift (cm−1)
3061
3083
3013
2968
2954
2922
2893
2857

FIG. 73

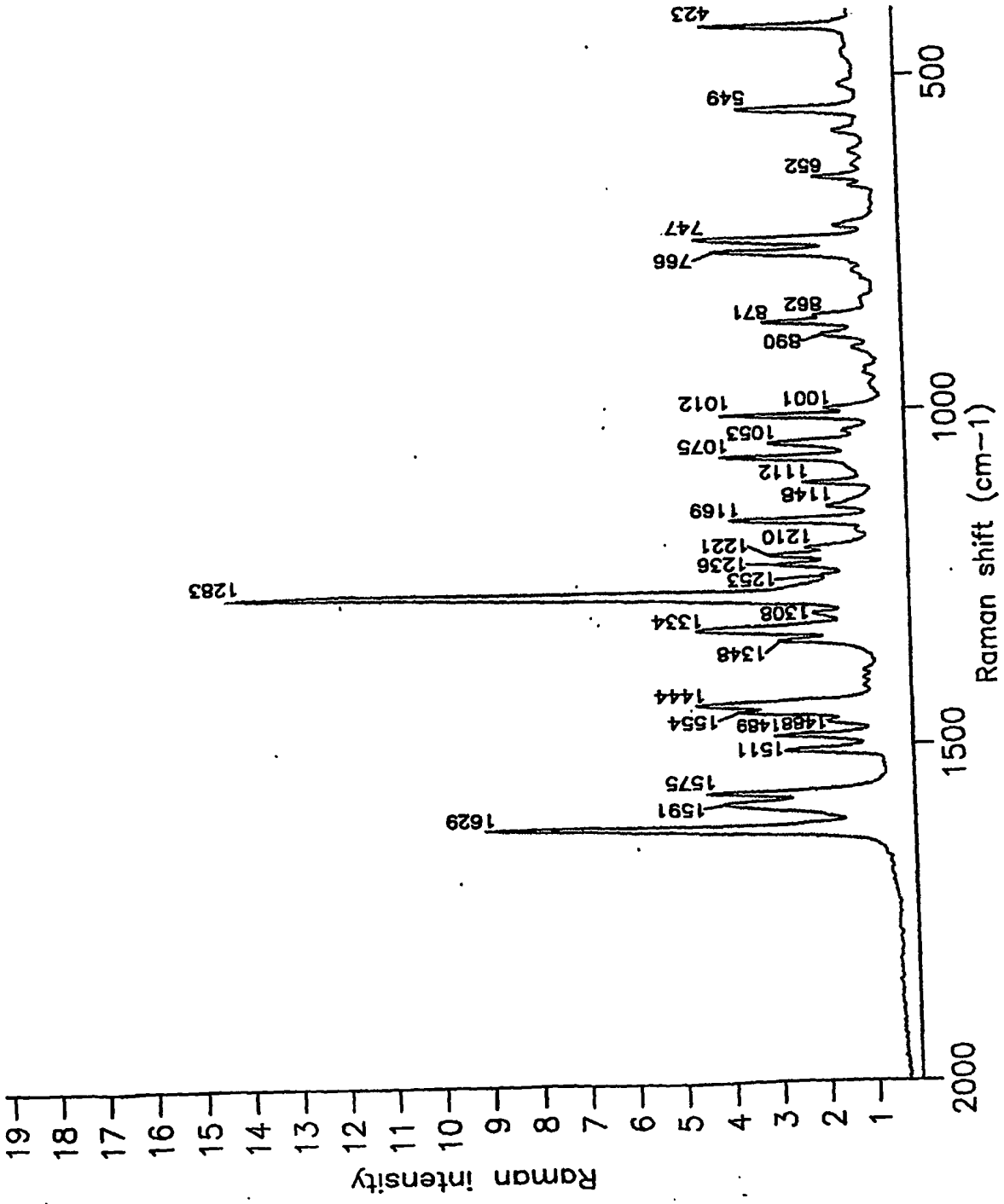

Raman intensity
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
2000
1500
1000
500
Raman shift (cm−1)
423
549
652
747
766
862
871
890
1001
1012
1053
1075
1112
1148
1169
1210
1221
1236
1253
1283
1308
1334
1348
1444
1468
1489
1554
1511
1575
1591
1629

FIG. 74

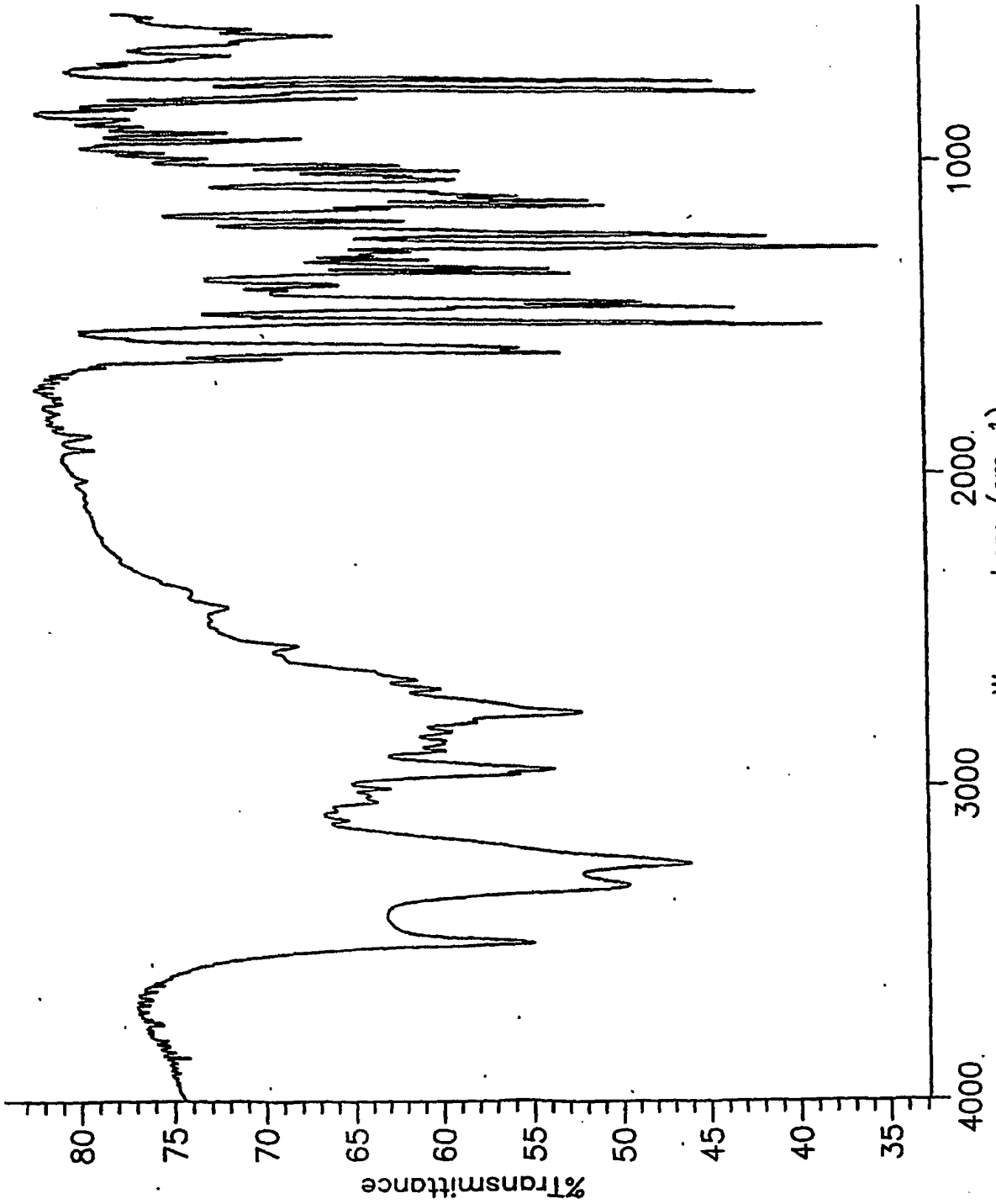

%Transmittance
80
75
70
65
60
55
50
45
40
35
4000
3000
2000
1000
Wavenumbers (cm-1)

FIG. 75

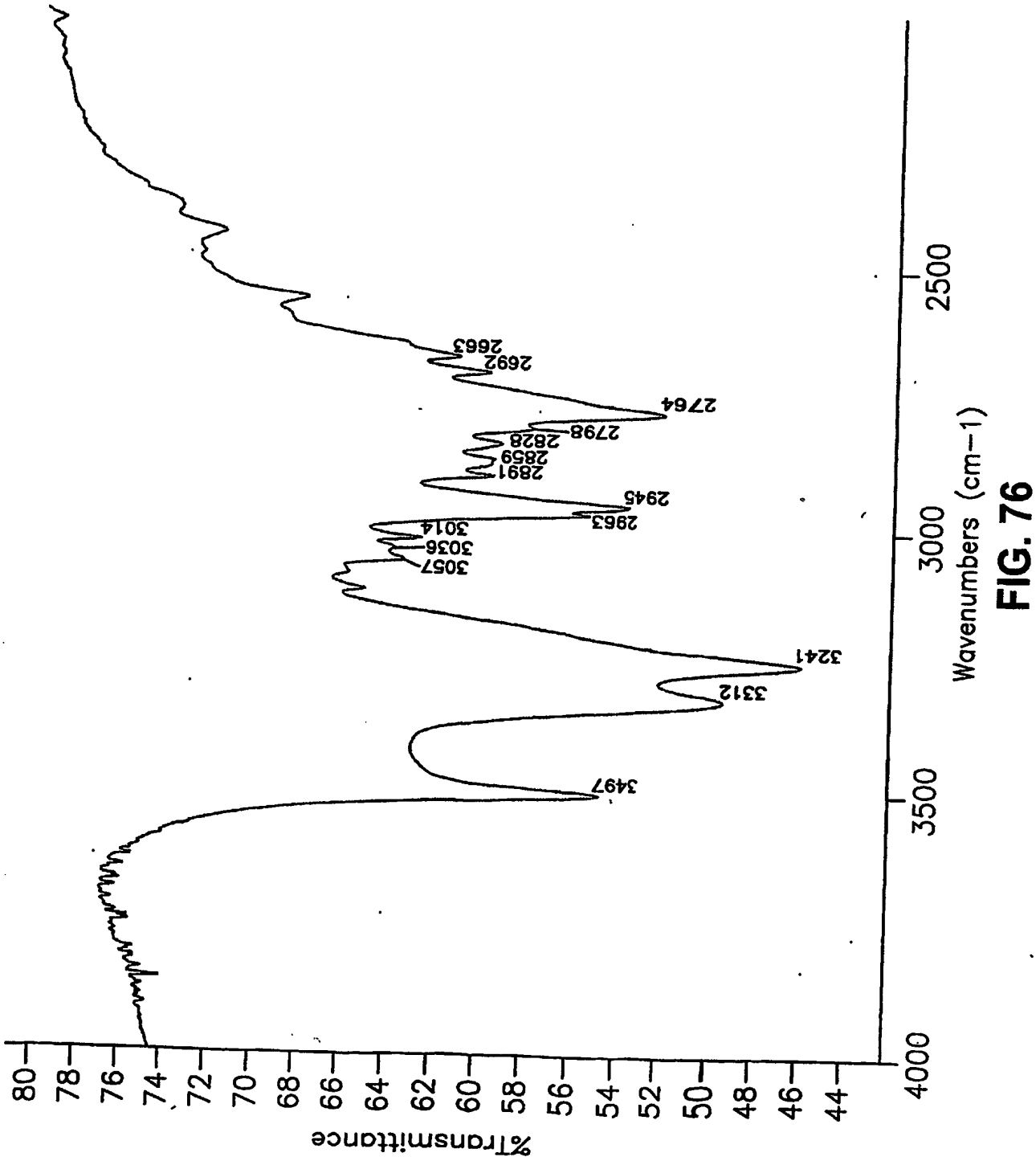

%Transmittance
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
4000
3500
3000
2500
Wavenumbers (cm−1)
3497
3312
3241
3057
3036
3014
2963
2945
2891
2859
2828
2798
2764
2692
2663

FIG. 76

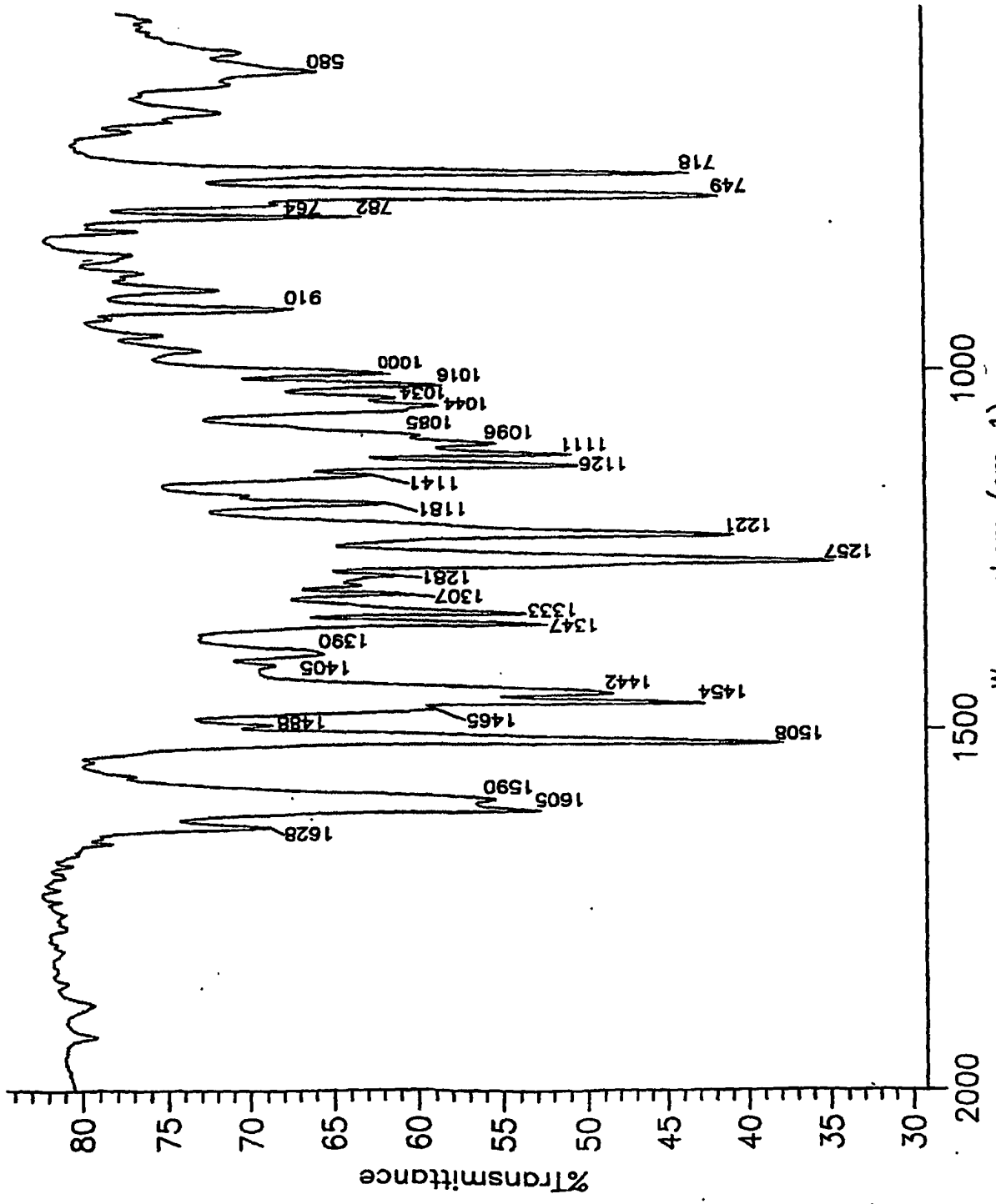

580
718
749
782
764
910
1000
1016
1034
1044
1085
1096
1111
1126
1141
1181
1221
1257
1281
1307
1333
1347
1390
1405
1442
1454
1465
1488
1508
1590
1605
1628
%Transmittance
80
75
70
65
60
55
50
45
40
35
30
Wavenumbers (cm−1)
2000
1500
1000

FIG. 77

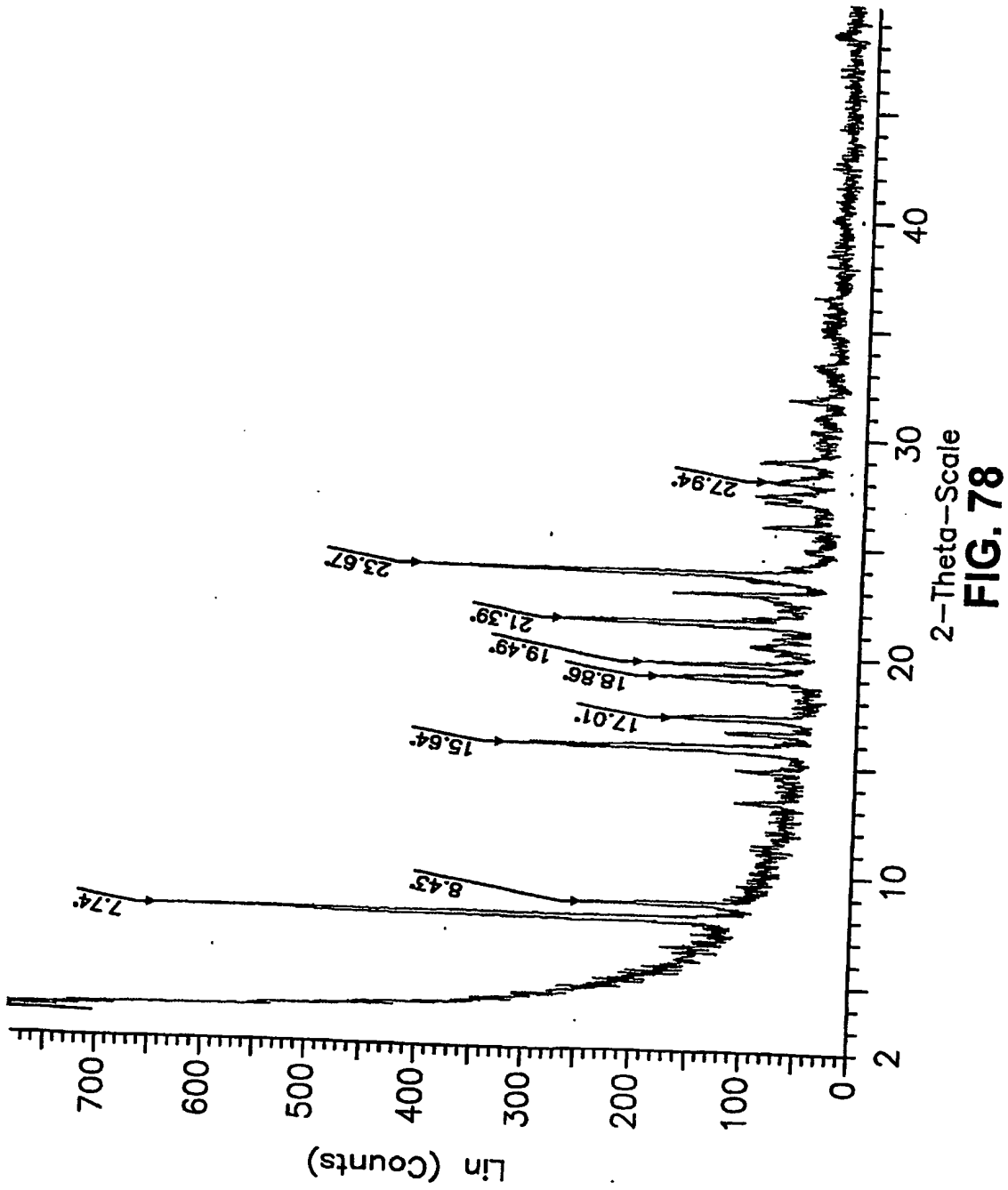

Lin (Counts)
700
600
500
400
300
200
100
0
2
10
20
30
40
2-Theta-Scale
7.74°
8.43°
15.64°
17.01°
18.86°
19.49°
21.39°
23.67°
27.94°

FIG. 78

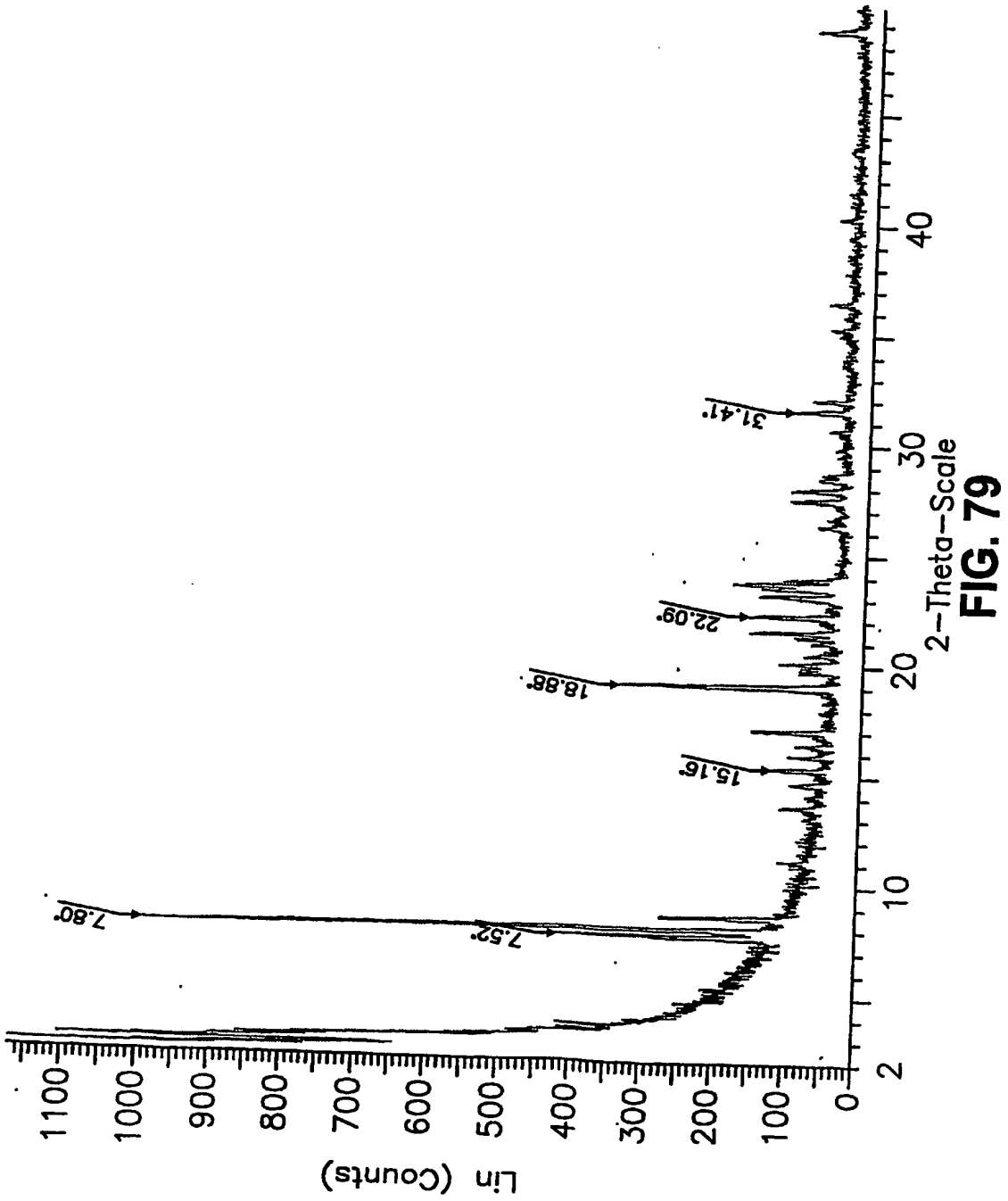

Lin (Counts)
1100
1000
900
800
700
600
500
400
300
200
100
0
2
10
20
30
40
2-Theta-Scale
7.80°
7.52°
15.16°
18.88°
22.09°
31.41°

FIG. 79

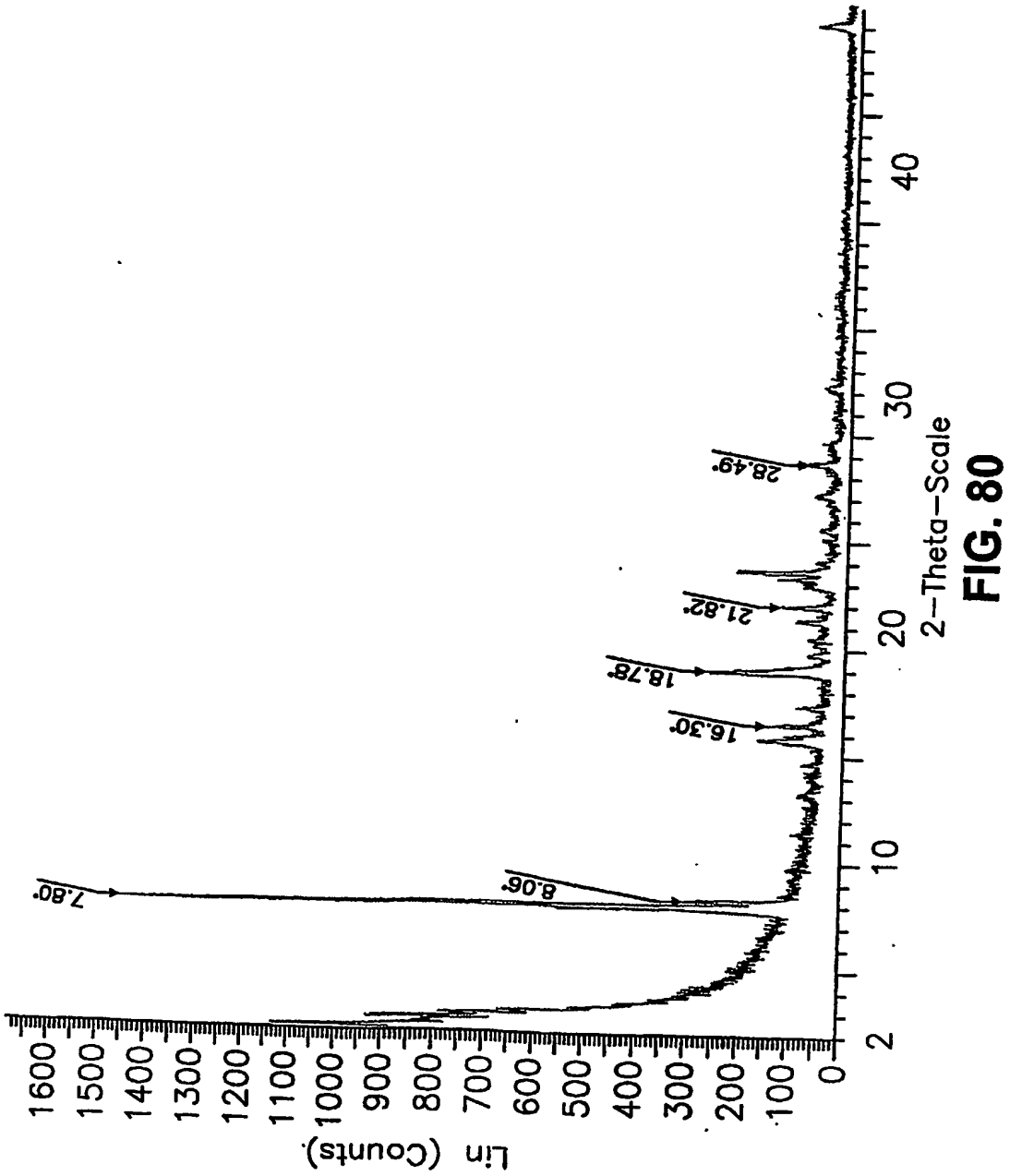

Lin (Counts)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
2
10
20
30
40
2-Theta-Scale
7.80°
8.06°
16.30°
18.78°
21.82°
28.49°

FIG. 80

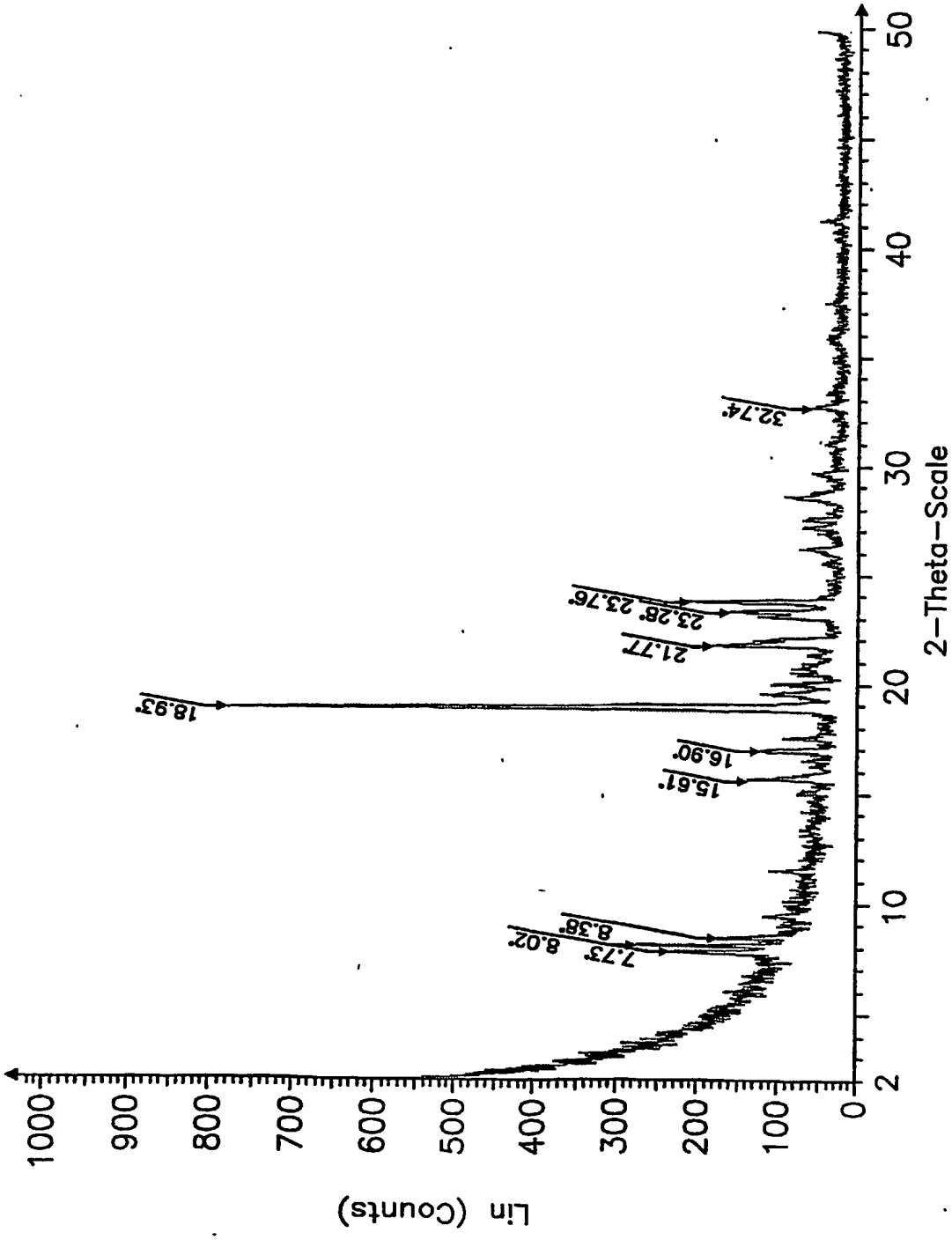

Lin (Counts)
1000
900
800
700
600
500
400
300
200
100
0
2
10
20
30
40
50
2-Theta-Scale
18.93°
16.90°
15.61°
8.38°
8.02°
7.73°
21.77°
23.28°
23.76°
32.74°

FIG. 81

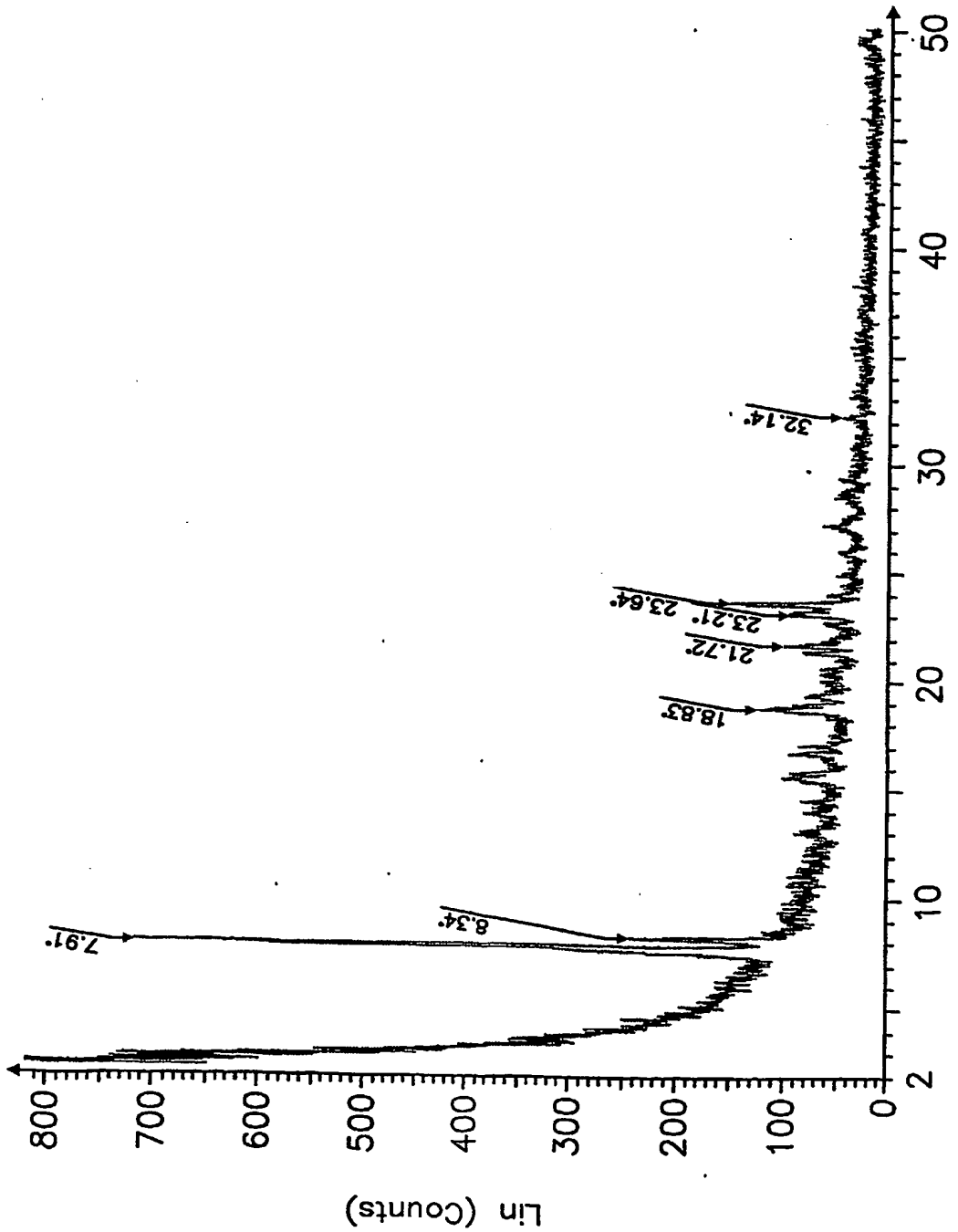

Lin (Counts)
800
700
600
500
400
300
200
100
0
2
10
20
30
40
50
2-Theta-Scale
7.91°
8.34°
18.83°
21.72°
23.21°
23.64°
32.14°

FIG. 82

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/20346

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/403; C07D 209/88
US CL : 514/411; 548/444, 440
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/411; 548/444, 440

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/00216 A1 (TEVA PHARMACEUTICAL INDUSTRIES LTD) 03 January 2002 (03.01.2002), page 15, line 6 to page 17, line 8.	1-40
A	WO 99/05105 A1 (BOEHRINGER MANHEIM GMBH) 04 February 1999(04.02.1999), see whole document.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search
10 October 2003 (10.10.2003)

Date of mailing of the international search report
05 DEC 2003

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Form PCT/ISA/210 (second sheet) (July 1998)